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(54) Title: PLATELET ADP RECEPTOR INHIBITORS

(57) Abstract: Novel compounds of formulae (I) to (VIII), which more particularly include sulfonylurea derivatives, sulfonylthiourea derivatives, sulfonylguanidine derivatives, sulfonylcyanoguanidine derivatives, thioacylsulfonamide derivatives, and acylsulfonamide derivatives which are effective platelet ADP receptor inhibitors. These derivatives may be used in various pharmaceutical compositions, and are particularly effective for the prevention and/or treatment of cardiovascular diseases, particularly those diseases related to thrombosis. The invention also relates to a method for preventing or treating thrombosis in a mammal comprising the step of administering a therapeutically effective amount of a compound of formulae (I) to (VIII), or a pharmaceutically acceptable salt thereof.

PATENT APPLICATION OF

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for

PLATELET ADP RECEPTOR INHIBITORS

PLATELET ADP RECEPTOR INHIBITORS

This application claims the benefit of U.S. Application No. 09/920,325, filed August 2, 2001, the disclosure of which is hereby incorporated by reference in its entirety for all purposes.

Field of the Invention

The invention relates to novel compounds of formula (I), formula (II), formula (III), formula (IV), formula (V), formula (VI), formula (VII) and formula (VIII) (hereinafter referred to as "formulae (I)-(VIII)"), which more particularly include sulfonylurea derivatives, sulfonylthiourea derivatives, sulfonylguanidine derivatives, sulfonylcyanoguanidine derivatives, thioacylsulfonamide derivatives, and acylsulfonamide derivatives which are effective platelet ADP receptor inhibitors. These derivatives may be used in various pharmaceutical compositions, and are particularly effective for the prevention and/or treatment of cardiovascular diseases, particularly those diseases related to thrombosis.

Description of the Related Art

Thrombotic complications are a major cause of death in the industrialized world. Examples of these complications include acute myocardial infarction, unstable angina, chronic stable angina, transient ischemic attacks, strokes, peripheral vascular disease, preeclampsia/eclampsia, deep venous thrombosis, embolism, disseminated intravascular coagulation and thrombotic cytopenic purpura. Thrombotic and restenotic complications also occur following invasive procedures, e.g., angioplasty, carotid endarterectomy, post CABG (coronary artery bypass graft) surgery, vascular graft surgery, stent placements and insertion of endovascular devices and prostheses. It is generally thought that platelet aggregates play a critical role in these events. Blood platelets, which normally circulate freely in the vasculature, become activated and aggregate to form a thrombus with

disturbed blood flow caused by ruptured atherosclerotic lesions or by invasive treatments such as angioplasty, resulting in vascular occlusion. Platelet activation can be initiated by a variety of agents, e.g., exposed subendothelial matrix molecules such as collagen, or by thrombin which is formed in the coagulation cascade.

An important mediator of platelet activation and aggregation is ADP (adenosine 5'-diphosphate) which is released from blood platelets in the vasculature upon activation by various agents, such as collagen and thrombin, and from damaged blood cells, endothelium or tissues. Activation by ADP results in the recruitment of more platelets and stabilization of existing platelet aggregates. Platelet ADP receptors mediating aggregation are activated by ADP and some of its derivatives and antagonized by ATP (adenosine 5'-triphosphate) and some of its derivatives (Mills, D.C.B. (1996) *Thromb. Hemost.* 76:835-856). Therefore, platelet ADP receptors are members of the family of P2 receptors activated by purine and/or pyrimidine nucleotides (King, B.F., Townsend-Nicholson, A. & Burnstock, G. (1998) *Trends Pharmacol. Sci.* 19:506-514).

Recent pharmacological data using selective antagonists suggests that ADP-dependent platelet aggregation requires activation of at least two ADP receptors (Kunapuli, S.P. (1998), *Trends Pharmacol. Sci.* 19:391-394; Kunapuli, S.P. & Daniel, J.L. (1998) *Biochem. J.* 336:513-523; Jantzen, H.M. et al. (1999) *Thromb. Hemost.* 81:111-117). One receptor appears to be identical to the cloned $P2Y_1$ receptor, mediates phospholipase C activation and intracellular calcium mobilization and is required for platelet shape change. The second platelet ADP receptor important for aggregation mediates inhibition of adenylyl cyclase. Molecular cloning of the gene or cDNA for this receptor ($P2Y_{12}$) has recently been reported (Hollopeter, G. et. al. (2001) *Nature* 409:202-207). Based on its pharmacological and signaling properties this receptor has been previously termed $P2Y_{ADP}$ (Fredholm, B.B. et al. (1997) *TIPS* 18:79-82), $P2T_{AC}$ (Kunapuli, S.P. (1998), *Trends Pharmacol. Sci.* 19:391-394) or P2Ycyc (Hechler, B. et al. (1998) Blood 92, 152-159).

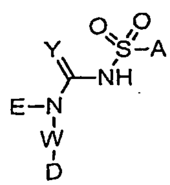
Various directly or indirectly acting synthetic inhibitors of ADP-dependent platelet aggregation with antithrombotic activity have been reported. The orally active

antithrombotic thienopyridines ticlopidine and clopidogrel inhibit ADP-induced platelet aggregation, binding of radiolabeled ADP receptor agonist 2-methylthioadenosine 5'-diphosphate to platelets, and other ADP-dependent events indirectly, probably via formation of an unstable and irreversible acting metabolite (Quinn, M.J. & Fitzgerald, D.J. (1999) Circulation 100:1667-1667). Some purine derivatives of the endogenous antagonist ATP, e.g., AR-C (formerly FPL or ARL) 67085MX and AR-C69931MX, are selective platelet ADP receptor antagonists which inhibit ADP-dependent platelet aggregation and are effective in animal thrombosis models (Humphries et al. (1995), *Trends Pharmacol. Sci.* 16, 179; Ingall, A.H. et al. (1999) J. Med. Chem. 42, 213-230). Novel triazolo [4,5-d] pyrimidine compounds have been disclosed as P_{2T} – antagonists (WO 99/05144). Tricyclic compounds as platelet ADP receptor inhibitors have also been disclosed in WO 99/36425. The target of these antithrombotic compounds appears to be the platelet ADP receptor mediating inhibition of adenylyl cyclase.

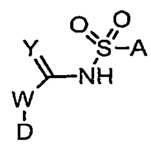
Despite these compounds, there exists a need for more effective platelet ADP receptor inhibitors. In particular, there is a need for platelet ADP receptor inhibitors having antithrombotic activity that are useful in the prevention and/or treatment of cardiovascular diseases, particularly those related to thrombosis.

Summary of the Invention

The invention provides compounds of formula (I), formula (II), formula (III), formula (IV), formula (V), formula (VI), formula (VII) and formula (VIII):



I



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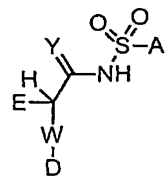

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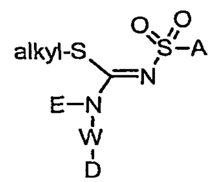

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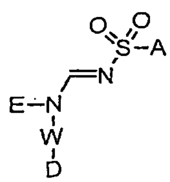

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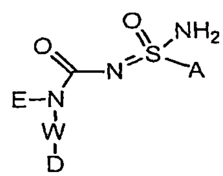

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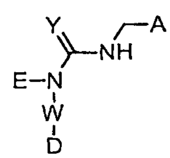

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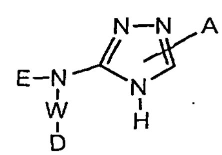


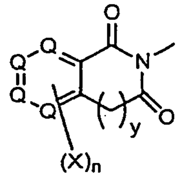
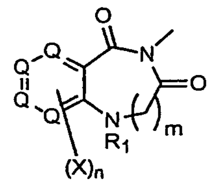
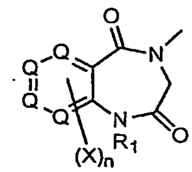
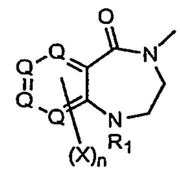
VIII

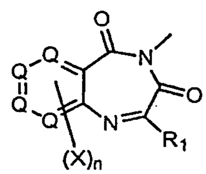
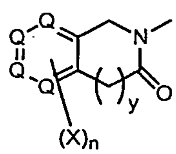
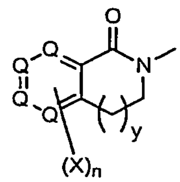
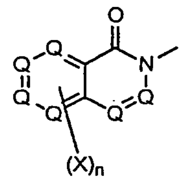
A is selected from the group consisting of aryl, substituted aryl, heteroaryl, substituted heteroaryl, alkylaryl, and alkylheteroaryl.

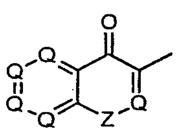
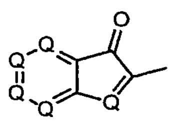
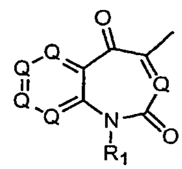
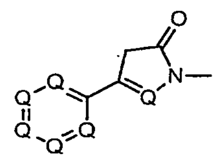
W is selected from the group consisting of aryl, substituted aryl, heteroaryl, and substituted heteroaryl.

E is selected from the group consisting of H, $-C_1-C_8$ alkyl, polyhaloalkyl, $-C_{3-8}$-cycloalkyl, aryl, alkylaryl, substituted aryl, heteroaryl, and substituted heteroaryl.

D is selected from the group consisting of NR^1-(C=O)-R^2 , -O-R^1;

 ,  ,  , 

 ,  ,  , 

 ,  ,  and 

wherein:

R^1 is independently selected from the group consisting of:

H, C_1-C_8 alkyl, polyhaloalkyl, -C_{3-8}-cycloalkyl, aryl, alkylaryl, substituted aryl, heteroaryl, substituted heteroaryl, -(C=O)-C_1-C_8 alkyl, -(C=O)-aryl, -(C=O)-substituted aryl, -(C=O)-heteroaryl and -(C=O)-substituted heteroaryl;

R^2 is independently selected from the group consisting of aryl, substituted aryl, heteroaryl, substituted heteroaryl, or ,

R^1 and R^2 can be direct linked or can be indirectly linked through a carbon chain that is from 1 to about 8 carbon atoms in length,

n is 0-4,
m is 0 or 1,
y is 0-4 and

Q is independently C or N, with the proviso that when Q is a ring carbon atom, each ring carbon atom is independenty substituted by X.

X is in each case a member independently selected from the group consisting of:

H, halogen, polyhaloalkyl, $-OR^3$, $-SR^3$, -CN, $-NO_2$, $-SO_2R^3$, $-C_{1-10}$-alkyl, $-C_{3-8}$-cycloalkyl, aryl, aryl-substituted by 1-4 R^3 groups, amino, amino-C_{1-8}-alkyl, C_{1-3}-acylamino, C_{1-3}-acylamino-C_{1-8}-alkyl, C_{1-6}-alkylamino, C_{1-6}-alkylamino C_{1-8} alkyl, C_{1-6} dialkylamino, C_{1-6} dialkylamino C_{1-8} alkyl, C_{1-6} alkoxy, C_{1-6} alkoxy-C_{1-6}-alkyl, carboxy-C_{1-6}-alkyl, C_{1-3}-alkoxycarbonyl, C_{1-3}-alkoxycarbonyl- C_{1-6}-alkyl, carboxy C_{1-6} alkyloxy, hydroxy, hydroxy C_{1-6} alkyl, and a 5 to 10 membered fused or non-fused aromatic or nonaromatic heterocyclic ring system, having 1 to 4 heteroatoms independently selected from N, O, and S, with the proviso that the carbon and nitrogen atoms, when present in the heterocyclic ring system, are unsubstituted, mono- or di-substituted independently with 0-2 R^4 groups.

R^3 and R^4 are each independently selected from the group consisting of:

H, halogen, -CN, $-NO_2$, $-C_{1-10}$ alkyl, C_{3-8}-cycloalkyl, aryl, amino, amino-C_{1-8}-alkyl, C_{1-3}-acylamino, C_{1-3}-acylamino-C_{1-8}-alkyl, C_{1-6}-alkylamino, C_{1-6}-alkylamino C_{1-8} alkyl, C_{1-6} dialkylamino, C_{1-6} dialkylamino C_{1-8} alkyl, C_{1-6} alkoxy, C_{1-6} alkoxy-C_{1-6}-alkyl, carboxy-C_{1-6}-alkyl, C_{1-3}-alkoxycarbonyl, C_{1-3}-alkoxycarbonyl-C_{1-6}-alkyl, carboxy-C_{1-6}-alkyloxy, hydroxy, hydroxy-C_{1-6}-alkyl, -thio and thio-C_{1-6}-alkyl.

Y is selected from the group consisting of O, S, N-OR^5 , and NR^5,

wherein R^5 is selected from the group consisting of :

H, C_{1-10} alkyl, C_{3-8}-cycloalkyl, NR^2, and CN; and

Z is selected from the group consisting of NR^1 and O.

The invention also covers all pharmaceutically acceptable salts and prodrugs of the compounds of formulae (I)-(VIII).

In another aspect, the invention provides pharmaceutical compositions for preventing or treating thrombosis in a mammal containing a therapeutically effective amount of a compound of formulae (I)-(VIII) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier. The invention further provides a method for preventing or treating thrombosis in a mammal by administering a therapeutically effective amount of a compound of formulae (I)-(VIII) or a pharmaceutically acceptable salt thereof.

Detailed Description of the Invention

Definitions

In accordance with the present invention and as used herein, the following terms are defined with the following meanings, unless explicitly stated otherwise.

The term "alkenyl" refers to a trivalent straight chain or branched chain unsaturated aliphatic radical. The term "alkinyl" (or "alkynyl") refers to a straight or branched chain aliphatic radical that includes at least two carbons joined by a triple bond. If no number of carbons is specified, alkenyl and alkinyl each refer to radicals having from 2-12 carbon atoms.

The term "alkyl" refers to saturated aliphatic groups including straight-chain, branched-chain and cyclic groups having the number of carbon atoms specified, or if no number is specified, having up to about 12 carbon atoms. The term "cycloalkyl" as used herein refers to a mono-, bi-, or tricyclic aliphatic ring having 3 to about 14 carbon atoms and preferably 3 to about 7 carbon atoms.

The term "C_1-C_6 alkoxy" as used herein refers to an ether moiety whereby the oxygen is connected to a straight or branched chain of carbon atoms of the number indicated.

The term "mono-C_1-C_6 alkylamino" as used herein refers to an amino moiety whereby the nitrogen is substituted with one H and one C_1-C_6 alkyl substituent, the latter being defined as above.

The term "di-C_1-C_6 alkylamino" as used herein refers to an amino moiety whereby the nitrogen is substituted with two C_1-C_6 alkyl substituents as defined above.

The term "monoarylamino" as used herein refers to an amino moiety whereby the nitrogen is substituted with one H and one aryl substituent, such as a phenyl, the latter being defined as above.

The term "diarylamino" as used herein refers to an amino moiety whereby the nitrogen is substituted with two aryl substituents, such as phenyl, the latter being defined as above.

The term "C_1-C_6 alkylsulfonyl" as used herein refers to a dioxosulfur moiety with the sulfur atom also connected to one C_1-C_6 alkyl substituent, the latter being defined as above.

The term "C_1-C_6 alkoxycarbonyl" as used herein refers to a hydroxycarbonyl moiety whereby the hydrogen is replaced by a C_1-C_6 alkyl substituent, the latter being defined as above.

As used herein, the terms "carbocyclic ring structure" and "C_{3-16} carbocyclic mono, bicyclic or tricyclic ring structure" or the like are each intended to mean stable ring structures having only carbon atoms as ring atoms wherein the ring structure is a substituted or unsubstituted member selected from the group consisting of: a stable monocyclic ring which is an aromatic ring ("aryl") having six ring atoms ("phenyl"); a stable monocyclic non-aromatic ring having from 3 to about 7 ring atoms in the ring; a stable bicyclic ring structure having a total of from 7 to about 12 ring atoms in the two rings wherein the bicyclic ring structure is selected from the group consisting of ring structures in which both of the rings are aromatic, ring structures in which one of the rings is aromatic and ring structures in which both of the rings are non-aromatic; and a stable tricyclic ring structure having a total of from about 10 to about 16 atoms in the three rings wherein the tricyclic ring structure is selected from the group consisting of:

ring structures in which three of the rings are aromatic, ring structures in which two of the rings are aromatic and ring structures in which three of the rings are non-aromatic. In each case, the non-aromatic rings when present in the monocyclic, bicyclic or tricyclic ring structure may independently be saturated, partially saturated or fully saturated. Examples of such carbocyclic ring structures include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, adamantyl, cyclooctyl, [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane (decalin), 2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, or tetrahydronaphthyl (tetralin). Moreover, the ring structures described herein may be attached to one or more indicated pendant groups via any carbon atom which results in a stable structure. The term "substituted" as used in conjunction with carbocyclic ring structures means that hydrogen atoms attached to the ring carbon atoms of ring structures described herein may be substituted by one or more of the substituents indicated for that structure if such substitution(s) would result in a stable compound.

The term "aryl" which is included with the term "carbocyclic ring structure" refers to an unsubstituted or substituted aromatic ring, substituted with one, two or three substituents selected from lower alkoxy, lower alkyl, lower alkylamino, hydroxy, halogen, cyano, hydroxyl, mercapto, nitro, thioalkoxy, carboxaldehyde, carboxyl, carboalkoxy and carboxamide, including but not limited to carbocyclic aryl, heterocyclic aryl, and biaryl groups and the like, all of which may be optionally substituted. Preferred aryl groups include phenyl, halophenyl, loweralkylphenyl, napthyl, biphenyl, phenanthrenyl and naphthacenyl.

The term "arylalkyl" which is included with the term "carbocyclic aryl" refers to one, two, or three aryl groups having the number of carbon atoms designated, appended to an alkyl group having the number of carbon atoms designated. Suitable arylalkyl groups include, but are not limited to, benzyl, picolyl, naphthylmethyl, phenethyl, benzyhydryl, trityl, and the like, all of which may be optionally substituted.

The term "phenyl" as used herein refers to a six carbon containing aromatic ring which can be variously mono- or poly-substituted with H, C_1-C_6 alkyl, hydroxyl, C_1-C_6 alkoxy, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, nitro, fluoro, chloro, bromo, iodo, hydroxycarbonyl, or C_1-C_6 alkoxycarbonyl.

As used herein, the term "heterocyclic ring" or "heterocyclic ring system" is

intended to mean a substituted or unsubstituted member selected from the group consisting of a stable monocyclic ring having from 5-7 members in the ring itself and having from 1 to 4 hetero ring atoms selected from the group consisting of N, O and S; a stable bicyclic ring structure having a total of from 7 to 12 atoms in the two rings wherein at least one of the two rings has from 1 to 4 hetero atoms selected from N, O and S, including bicyclic ring structures wherein any of the described stable monocyclic heterocyclic rings is fused to a hexane or benzene ring; and a stable tricyclic heterocyclic ring structure having a total of from 10 to 16 atoms in the three rings wherein at least one of the three rings has from 1 to 4 hetero atoms selected from the group consisting of N, O and S. Any nitrogen and sulfur atoms present in a heterocyclic ring of such a heterocyclic ring structure may be oxidized. Unless indicated otherwise the terms "heterocyclic ring" or "heterocyclic ring system" include aromatic rings, as well as non-aromatic rings which can be saturated, partially saturated or fully saturated non-aromatic rings. Also, unless indicated otherwise the term "heterocyclic ring system" includes ring structures wherein all of the rings contain at least one hetero atom as well as structures having less than all of the rings in the ring structure containing at least one hetero atom, for example bicyclic ring structures wherein one ring is a benzene ring and one of the rings has one or more hetero atoms are included within the term "heterocyclic ring systems" as well as bicyclic ring structures wherein each of the two rings has at least one hetero atom. Moreover, the ring structures described herein may be attached to one or more indicated pendant groups via any hetero atom or carbon atom which results in a stable structure. Further, the term "substituted" means that one or more of the hydrogen atoms on the ring carbon atom(s) or nitrogen atom(s) of the each of the rings in the ring structures described herein may be replaced by one or more of the indicated substituents if such replacement(s) would result in a stable compound. Nitrogen atoms in a ring structure may be quaternized, but such compounds are specifically indicated or are included within the term "a pharmaceutically acceptable salt" for a particular compound. When the total number of O and S atoms in a single heterocyclic ring is greater than 1, it is preferred that such atoms not be adjacent to one another. Preferably, there are no more that 1 O or S ring atoms in the same ring of a given heterocyclic ring structure.

Examples of monocylic and bicyclic heterocylic ring systems, in alphabetical order, are acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazalinyl, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2H,6H-1,5,2-

dithiazinyl, dihydrofuro[2,3-b]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl (benzimidazolyl), isothiazolyl, isoxazolyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyroazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pryidooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6H-1,2,5-thiadazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl and xanthenyl. Preferred heterocyclic ring structures include, but are not limited to, pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrrolidinyl, imidazolyl, indolyl, benzimidazolyl, 1H-indazolyl, oxazolinyl, or isatinoyl. Also included are fused ring and spiro compounds containing, for example, the above heterocylic ring structures.

As used herein the term "aromatic heterocyclic ring system" has essentially the same definition as for the monocyclic and bicyclic ring systems except that at least one ring of the ring system is an aromatic heterocyclic ring or the bicyclic ring has an aromatic or non-aromatic heterocyclic ring fused to an aromatic carbocyclic ring structure.

The terms "halo" or "halogen" as used herein refer to Cl, Br, F or I substituents. The term "haloalkyl", and the like, refer to an aliphatic carbon radicals having at least one hydrogen atom replaced by a Cl, Br, F or I atom, including mixtures of different halo atoms. Trihaloalkyl includes trifluoromethyl and the like as preferred radicals, for example.

The term "methylene" refers to $-CH_2-$.

The term "pharmaceutically acceptable salts" includes salts of compounds derived from the combination of a compound and an organic or inorganic acid. These compounds are useful in both free base and salt form. In practice, the use of the salt form

amounts to use of the base form; both acid and base addition salts are within the scope of the present invention.

"Pharmaceutically acceptable acid addition salt" refers to salts retaining the biological effectiveness and properties of the free bases and which are not biologically or otherwise undesirable, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicyclic acid and the like.

"Pharmaceutically acceptable base addition salts" include those derived from inorganic bases such as sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Particularly preferred are the ammonium, potassium, sodium, calcium and magnesium salts. Salts derived from pharmaceutically acceptable organic nontoxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-diethylaminoethanol, trimethamine, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperizine, piperidine, N-ethylpiperidine, polyamine resins and the like. Particularly preferred organic nontoxic bases are isopropylamine, diethylamine, ethanolamine, trimethamine, dicyclohexylamine, choline, and caffeine.

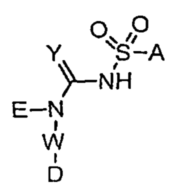
"Biological property" for the purposes herein means an *in vivo* effector or antigenic function or activity that is directly or indirectly performed by a compound of this invention that are often shown by *in vitro* assays. Effector functions include receptor or ligand binding, any enzyme activity or enzyme modulatory activity, any carrier binding activity, any hormonal activity, any activity in promoting or inhibiting adhesion of cells to an extracellular matrix or cell surface molecules, or any structural role. Antigenic functions include possession of an epitope or antigenic site that is capable of reacting with antibodies raised against it.

In the compounds of this invention, carbon atoms bonded to four non-identical substituents are asymmetric. Accordingly, the compounds may exist as diastereoisomers,

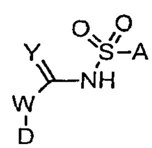
enantiomers or mixtures thereof. The syntheses described herein may employ racemates, enantiomers or diastereomers as starting materials or intermediates. Diastereomeric products resulting from such syntheses may be separated by chromatographic or crystallization methods, or by other methods known in the art. Likewise, enantiomeric product mixtures may be separated using the same techniques or by other methods known in the art. Each of the asymmetric carbon atoms, when present in the compounds of this invention, may be in one of two configurations (R or S) and both are within the scope of the present invention.

Compound Embodiments of the Invention

Compounds of formula (I), formula (II), formula (III), formula (IV), formula (V), formula (VI), formula (VII) and formula (VIII) below represent one embodiment of the invention:



I



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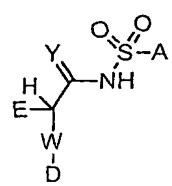

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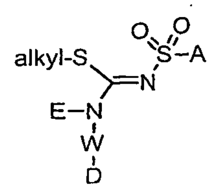

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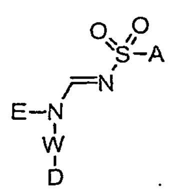

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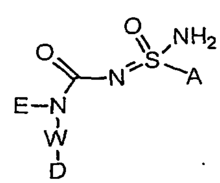

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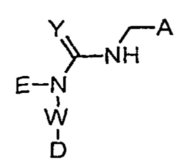

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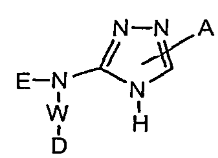


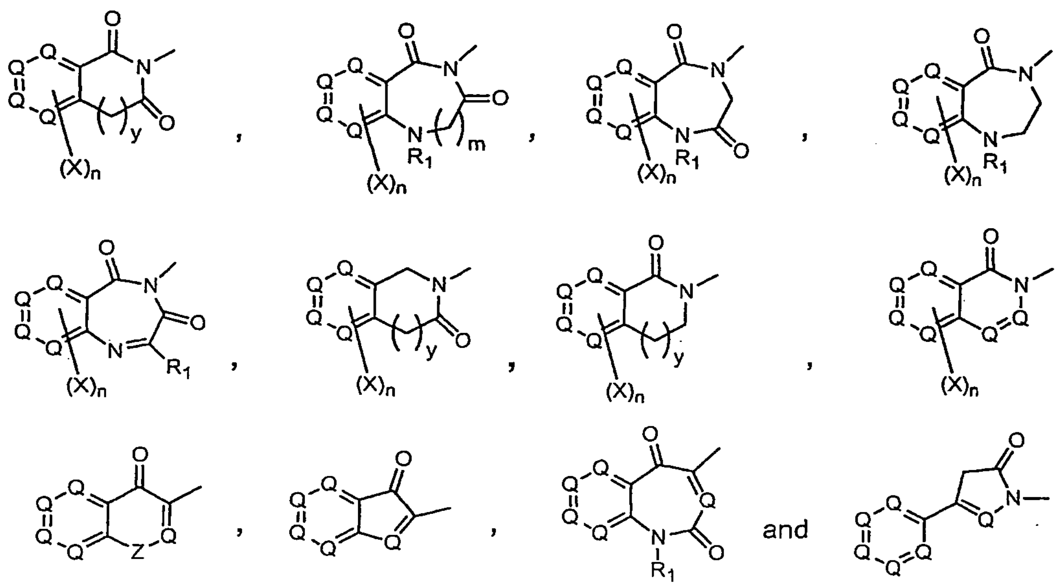
VIII

A is selected from the group consisting of aryl, substituted aryl, heteroaryl, substituted heteroaryl, alkylaryl, and alkylheteroaryl.

W is selected from the group consisting of aryl, substituted aryl, heteroaryl, and substituted heteroaryl.

E is selected from the group consisting of H, $-C_1-C_8$ alkyl, polyhaloalkyl, $-C_{3-8}$-cycloalkyl, aryl, alkylaryl, substituted aryl, heteroaryl, and substituted heteroaryl.

D is selected from the group consisting of NR^1-(C=O)-R^2, -O-R^1;



wherein:

R^1 is independently selected from the group consisting of:

H, C_1-C_8 alkyl, polyhaloalkyl, $-C_{3-8}$-cycloalkyl, aryl, alkylaryl, substituted aryl, heteroaryl, substituted heteroaryl, -(C=O)-C_1-C_8 alkyl, -(C=O)-aryl, -(C=O)-substituted aryl, -(C=O)-heteroaryl and -(C=O)-substituted heteroaryl;

R^2 is selected from the group consisting of: aryl, substituted aryl, heteroaryl, substituted heteroaryl, or

R^1 and R^2 can be direct linked or can be indirectly linked through a carbon chain that is from 1 to about 8 carbon atoms in length,

n is 0-4,
m is 0 or 1,
y is 0-4 and

Q is independently C or N, with the proviso that when Q is a ring carbon atom, each ring carbon atom is independently substituted by X, wherein

X is in each case a member independently selected from the group consisting of:

> H, halogen, polyhaloalkyl, $-OR^3$, $-SR^3$, -CN, $-NO_2$, $-SO_2R^3$, $-C_{1-10}$-alkyl, $-C_{3-8}$-cycloalkyl, aryl, aryl-substituted by 1-4 R^3 groups, amino, amino-C_{1-8}-alkyl, C_{1-3}-acylamino, C_{1-3}-acylamino-C_{1-8}-alkyl, C_{1-6}-alkylamino, C_{1-6}-alkylamino C_{1-8} alkyl, C_{1-6} dialkylamino, C_{1-6} dialkylamino C_{1-8} alkyl, C_{1-6} alkoxy, C_{1-6} alkoxy-C_{1-6}-alkyl, carboxy-C_{1-6}-alkyl, C_{1-3}-alkoxycarbonyl, C_{1-3}-alkoxycarbonyl- C_{1-6}-alkyl, carboxy C_{1-6} alkyloxy, hydroxy, hydroxy C_{1-6} alkyl, and a 5 to 10 membered fused or non-fused aromatic or nonaromatic heterocyclic ring system, having 1 to 4 heteroatoms independently selected from N, O, and S, with the proviso that the carbon and nitrogen atoms, when present in the heterocyclic ring system, are unsubstituted, mono- or di-substituted independently with 0-2 R^4 groups, and

wherein R^3 and R^4 are each independently selected from the group consisting of:

> H, halogen, -CN, $-NO_2$, $-C_{1-10}$ alkyl, C_{3-8}-cycloalkyl, aryl, amino, amino-C_{1-8}-alkyl, C_{1-3}-acylamino, C_{1-3}-acylamino-C_{1-8}-alkyl, C_{1-6}-alkylamino, C_{1-6}-alkylamino C_{1-8} alkyl, C_{1-6} dialkylamino, C_{1-6} dialkylamino C_{1-8} alkyl, C_{1-6} alkoxy, C_{1-6} alkoxy-C_{1-6}-alkyl, carboxy-C_{1-6}-alkyl, C_{1-3}-alkoxycarbonyl, C_{1-3}-alkoxycarbonyl-C_{1-6}-alkyl, carboxy-C_{1-6}-alkyloxy, hydroxy, hydroxy-C_{1-6}-alkyl, -thio and thio-C_{1-6}-alkyl.

Y is selected from the group consisting of O, S, N-OR^5 , and NR^5,

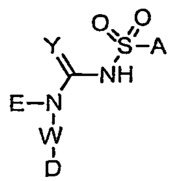
wherein R^5 is selected from the group consisting of :

> H, C_{1-10} alkyl, C_{3-8}-cycloalkyl, and CN; and

Z is selected from the group consisting of NR^1 and O.

The invention also covers all pharmaceutically acceptable salts and prodrugs of the compounds of formula I to formula VIII.

In a preferred embodiment of the invention, compounds of formulae (I) – (VIII)



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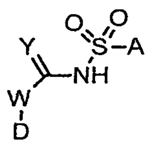

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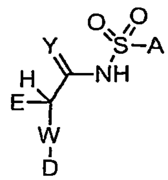

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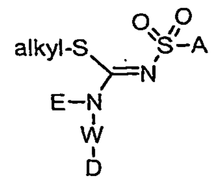

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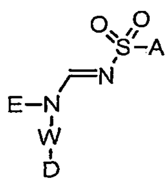

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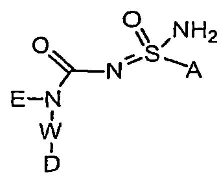

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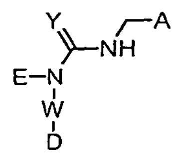

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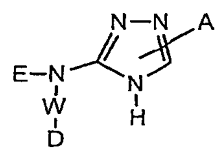
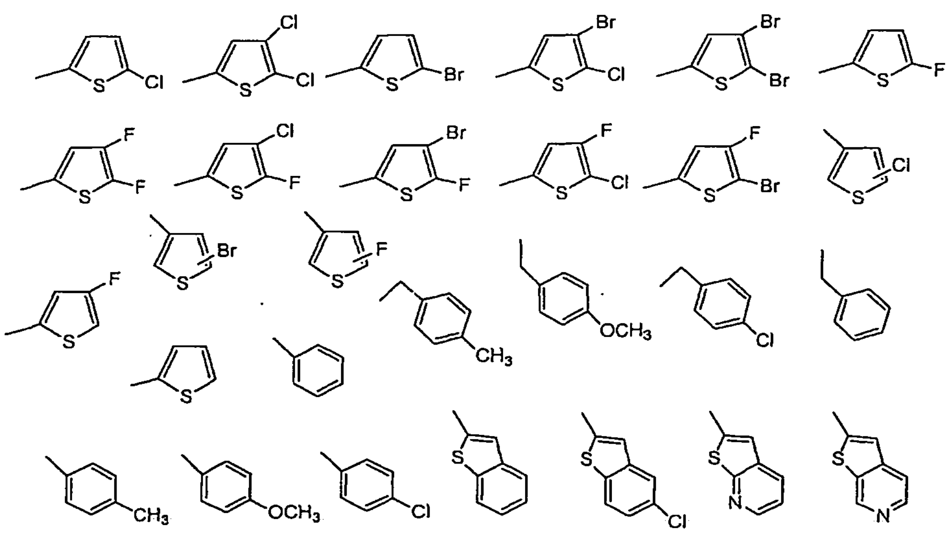


VIII

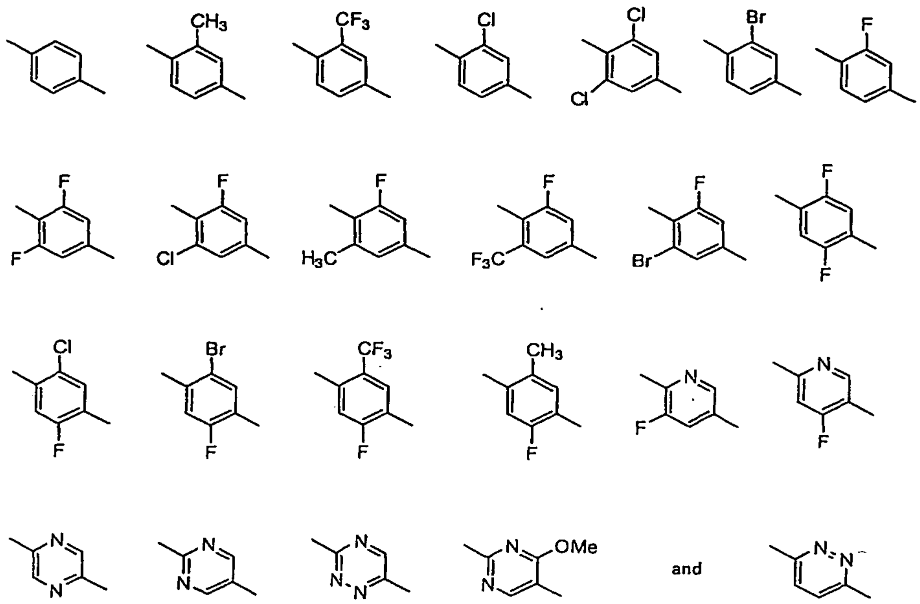
A is selected from the group consisting of:



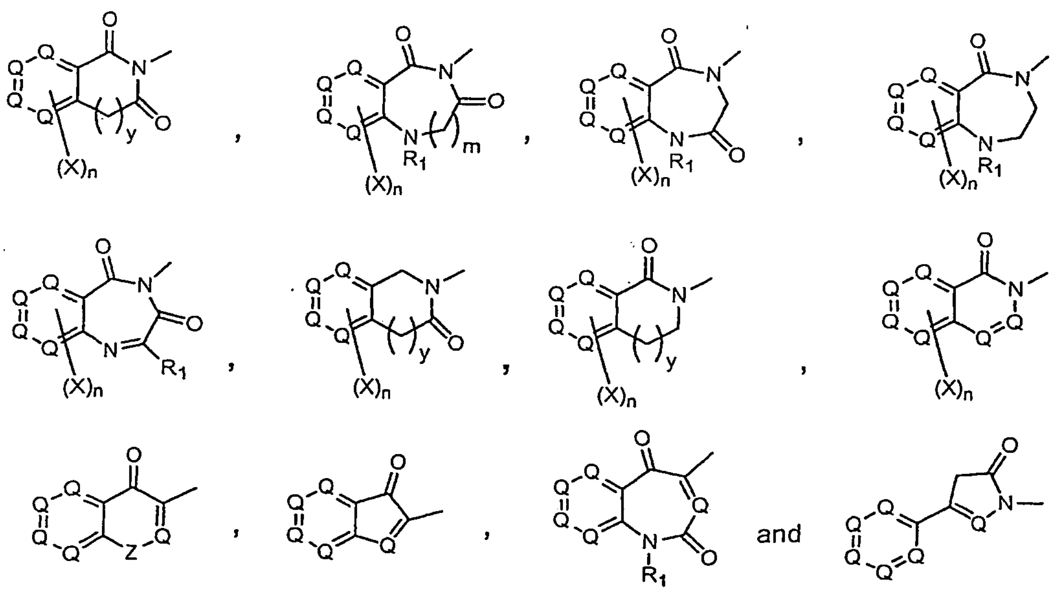
Y is selected from the group consisting of O, S, N-OR^5 and NR^5.

E is selected from the group consisting of H, or C_{1-8} alkyl.

W is selected from the group consisting of:

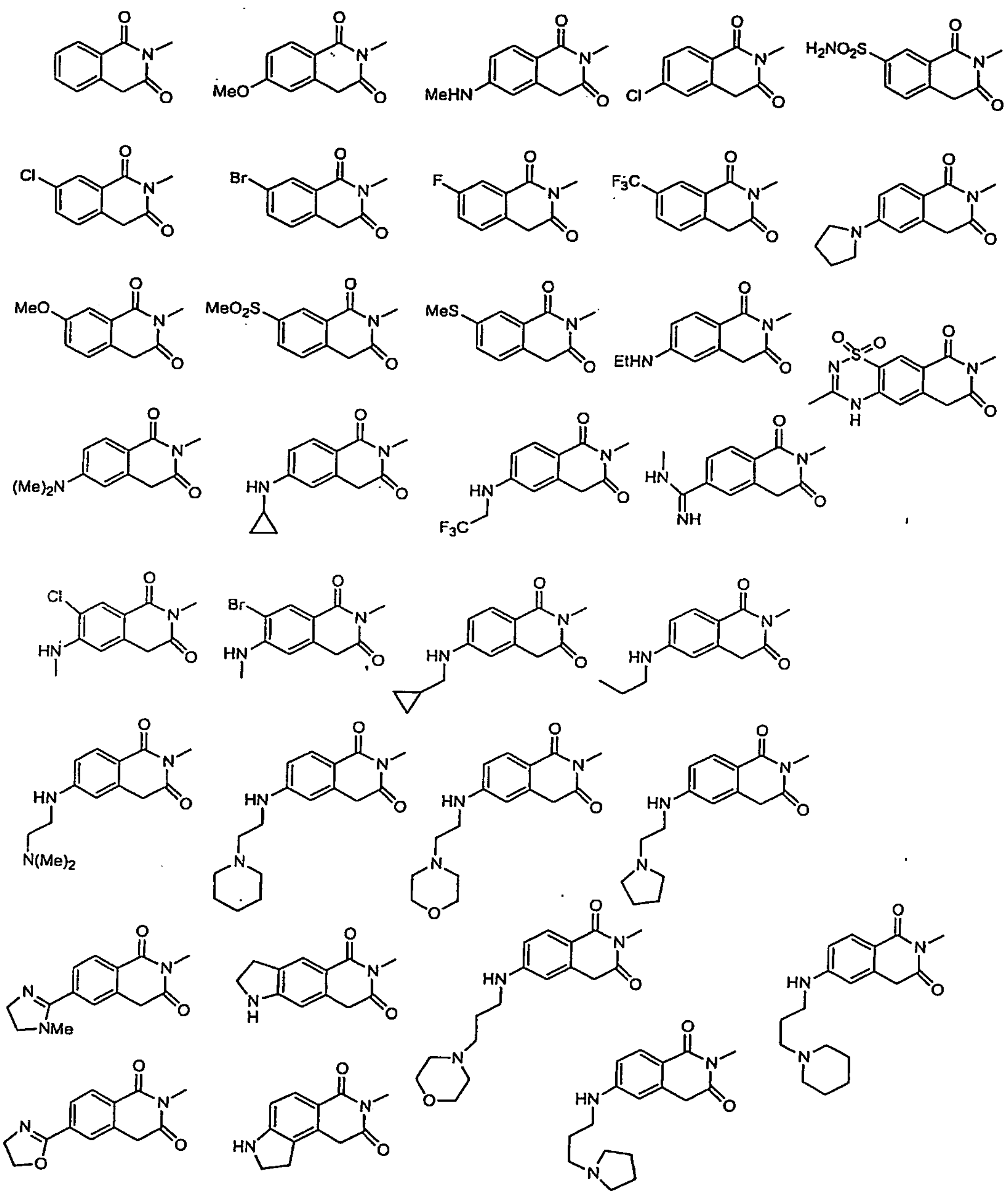


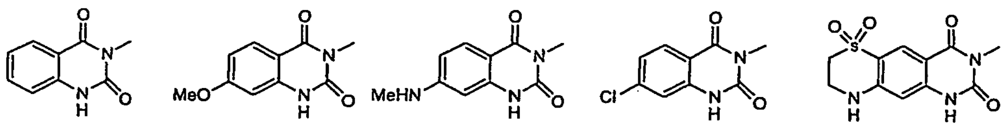
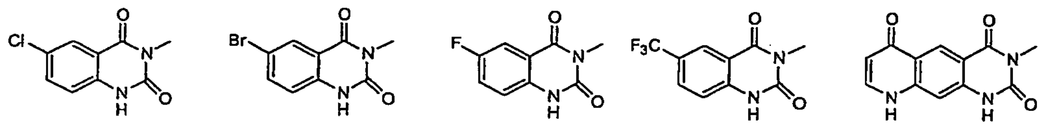
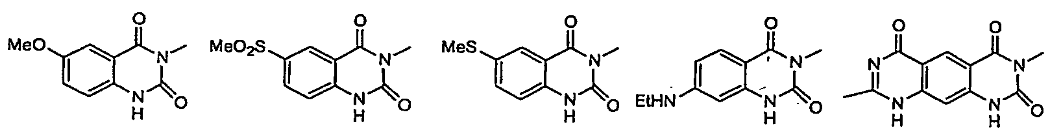
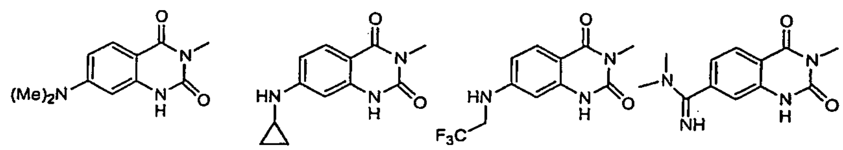
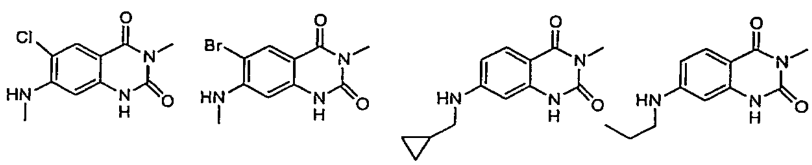
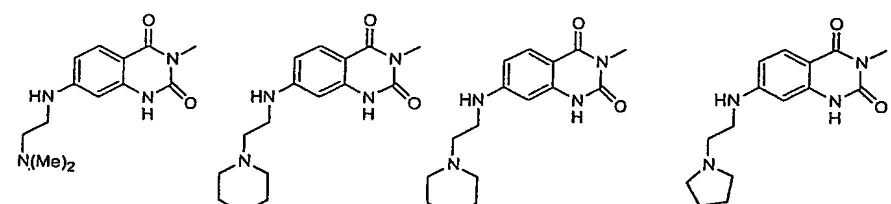
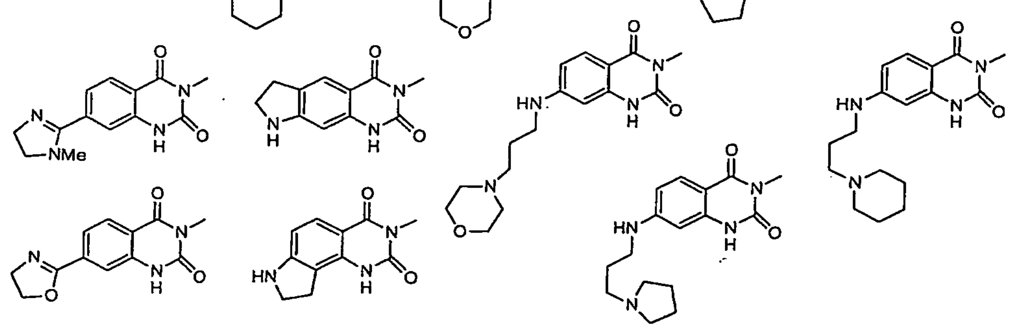
D is selected from the group consisting of :

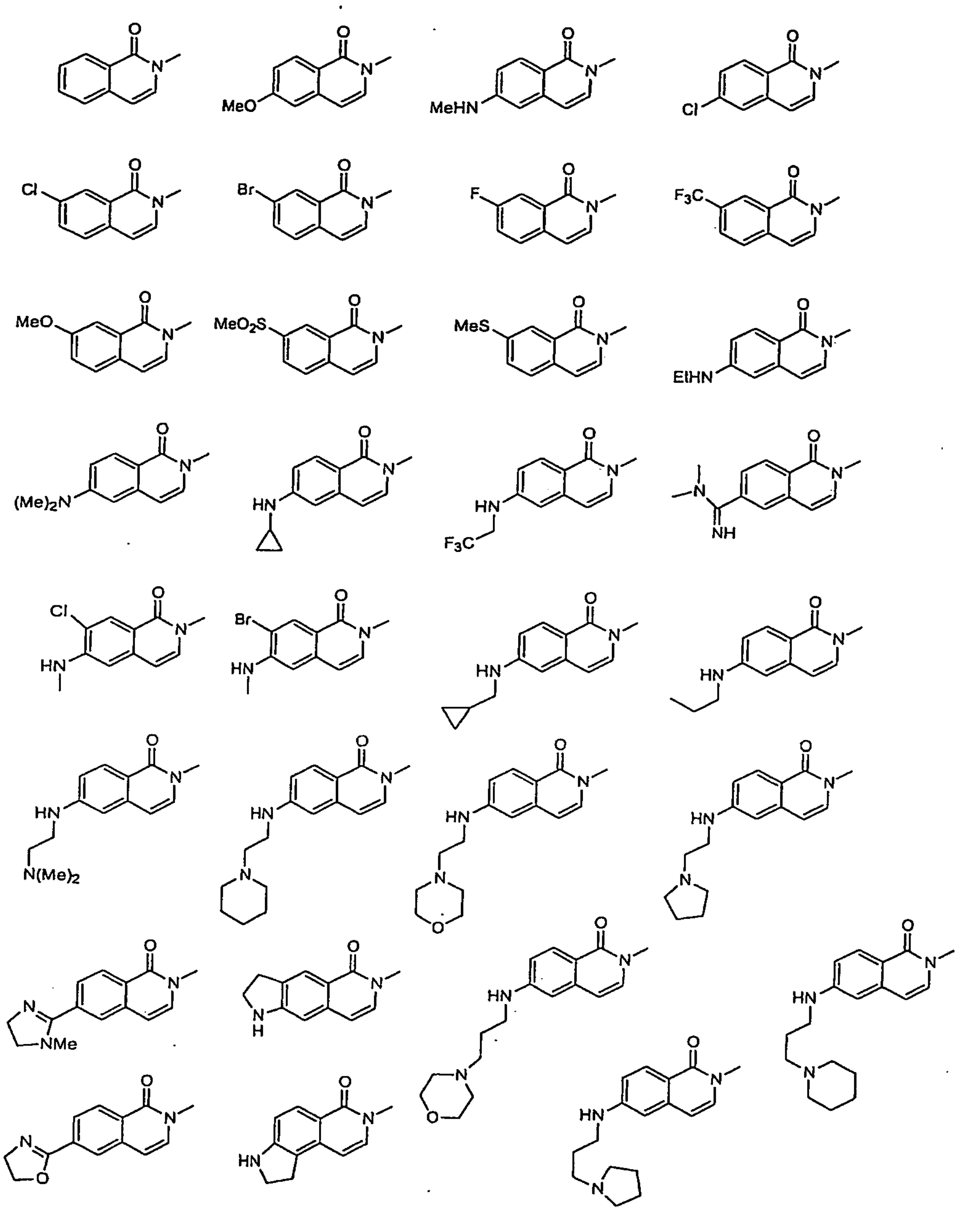


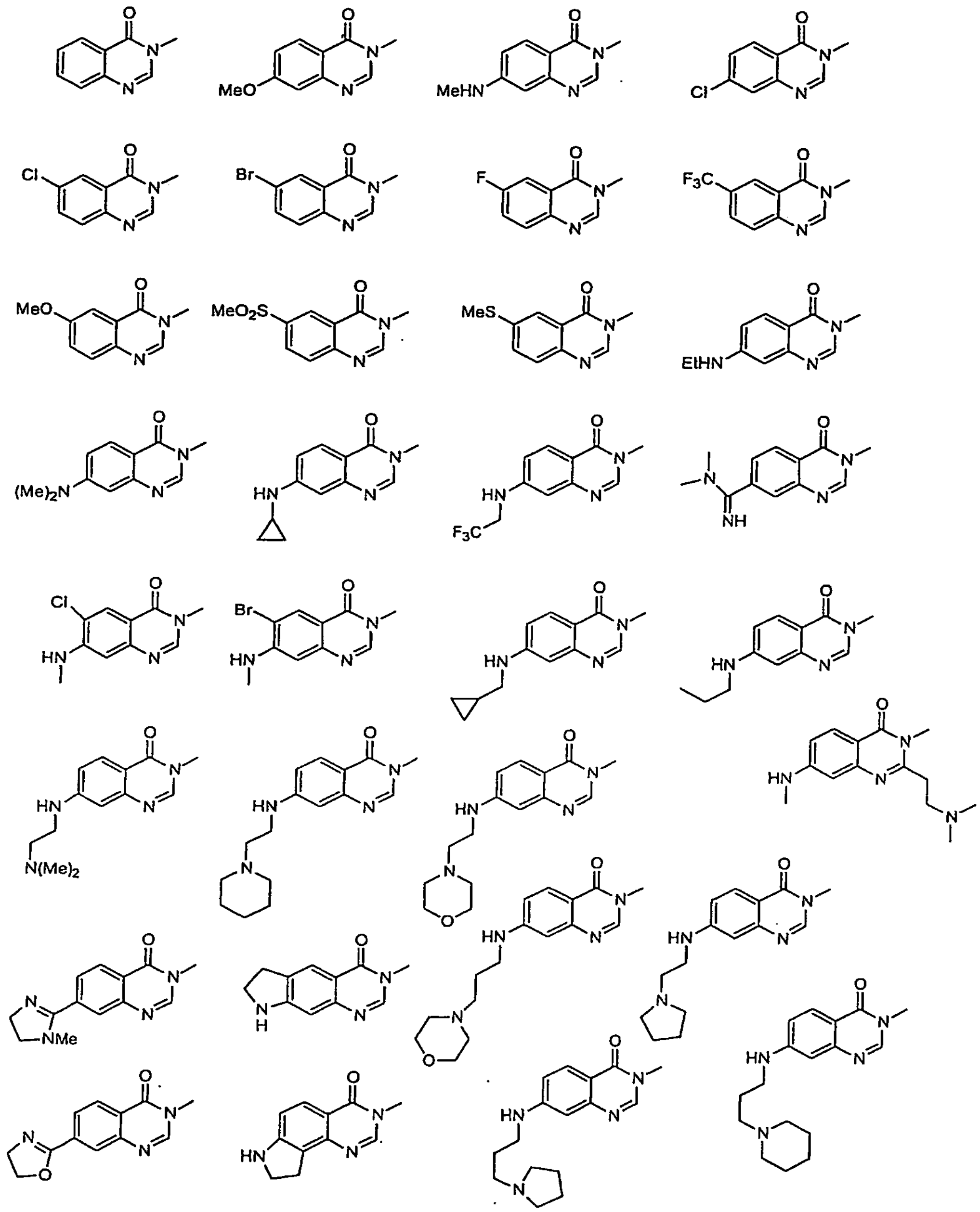
In a more preferred embodiment of the invention, compounds of formulae (I) to (VIII) include the compounds wherein:

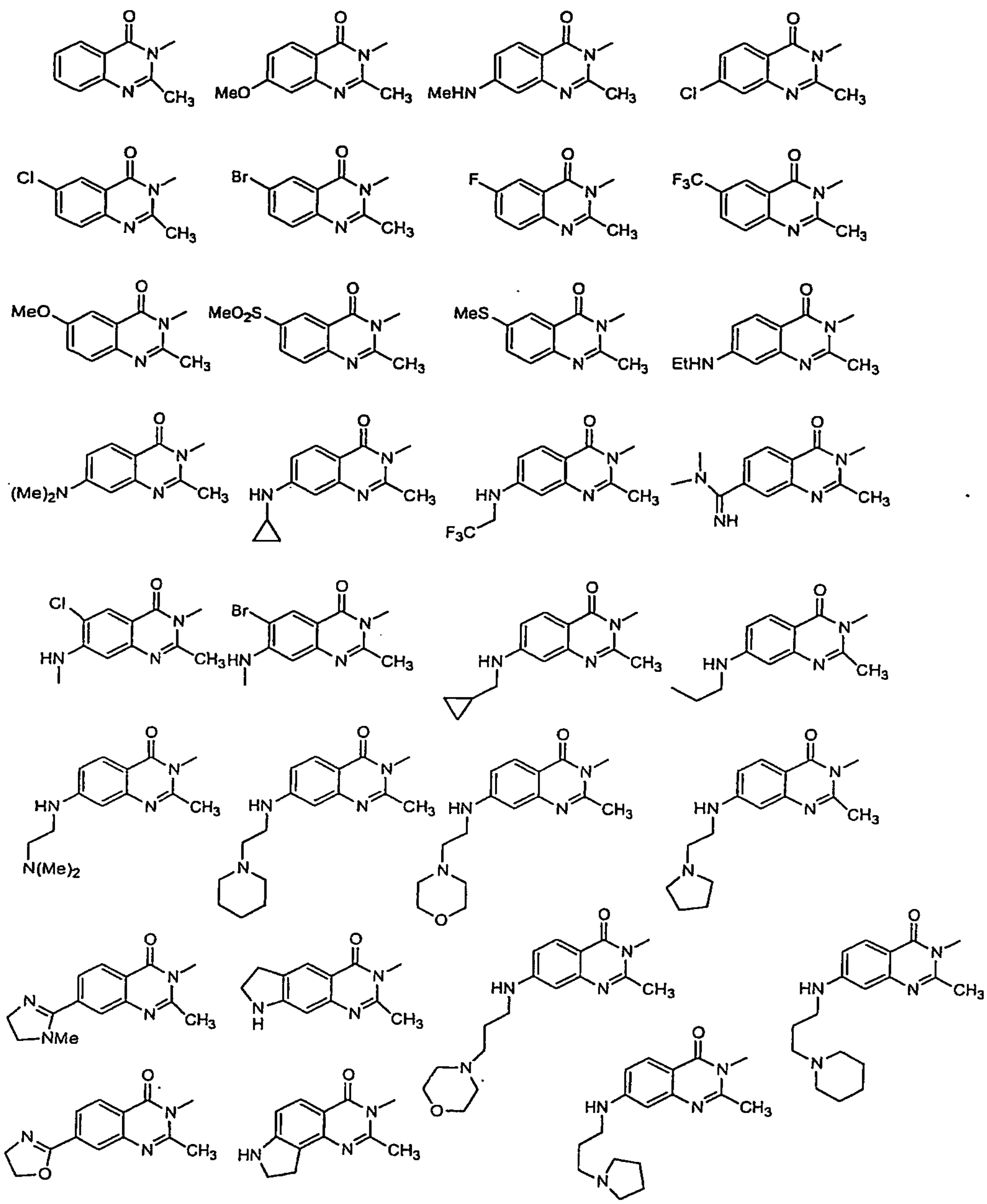
D is selected from the group consisting of:

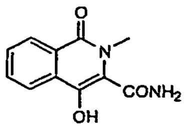
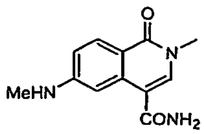
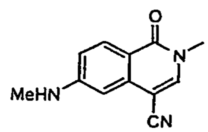
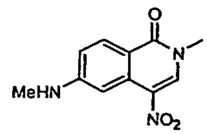
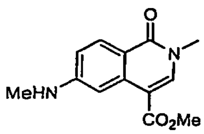
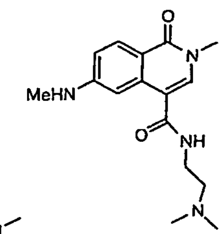
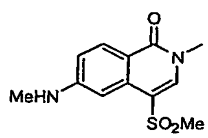
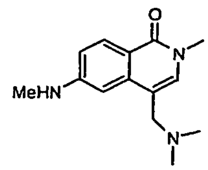
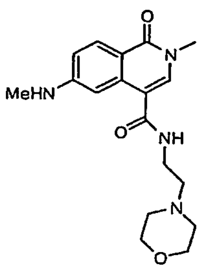
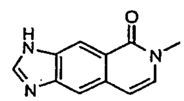
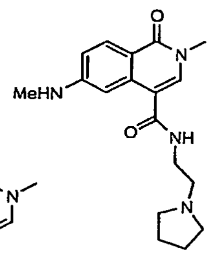
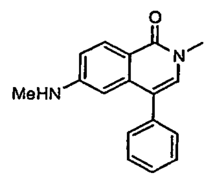
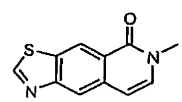
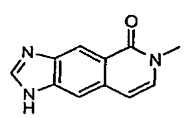
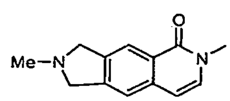
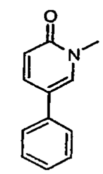
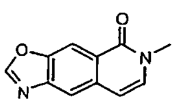
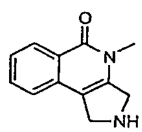
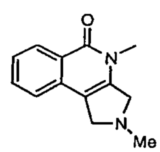




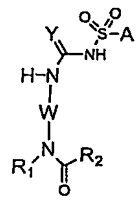




In another preferred embodiment of the invention, compounds of formulae (I)-(VI) include the compounds set forth below in Tables 1- 4:

Table 1



Formula Ia

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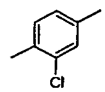
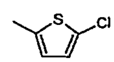
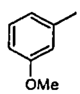
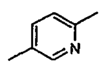
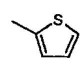
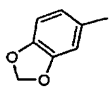
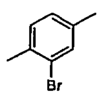
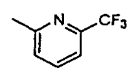
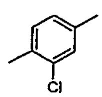
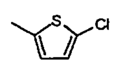
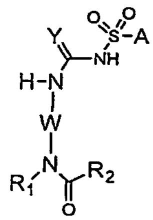
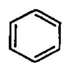
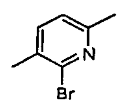
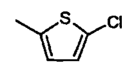
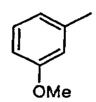
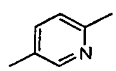
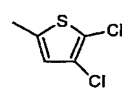
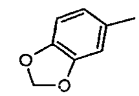
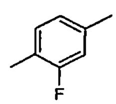
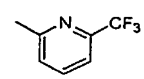
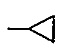
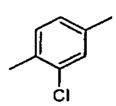
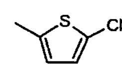
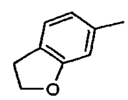
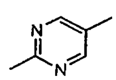
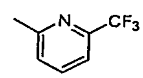
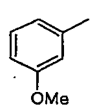
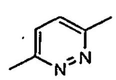
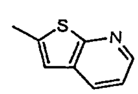
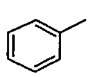
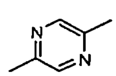
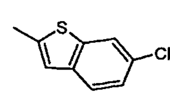
	H		O	
	H		O	
	H		S	
	H		$N-C\equiv N$	

Table 1 (cont.)



Formula Ia

R₂	R₁	W	Y	A
	H		O	
	H		NH	
	Me		NH	
			N-C≡N	
	Me		O	
	H		O	
	H		N-OH	

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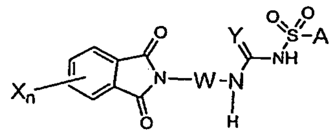
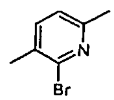
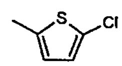
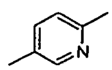
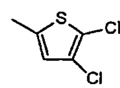
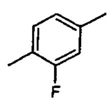
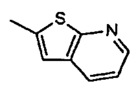
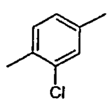
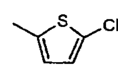
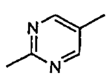
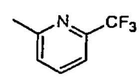
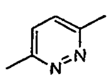
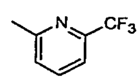
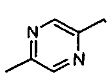
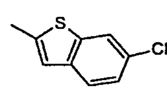
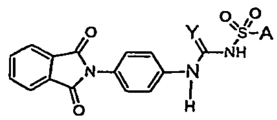


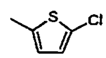
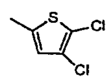
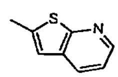
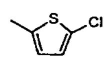
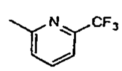
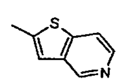
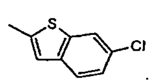
Formula Ib

X	W	Y	A
3-Br		O	
3-Cl		NH	
4-OMe		O	
H		N-C≡N	
3,4-diMe		NH	
3-SO_2Me		O	
3 -N(Me)Me		N-OH	

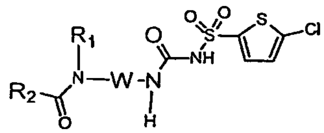
A. Table 3



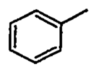
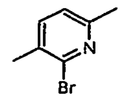
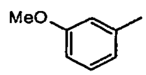
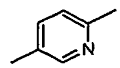
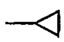
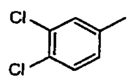
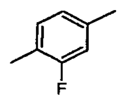
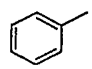
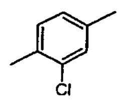
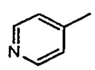
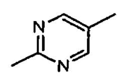
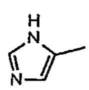
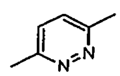
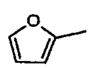
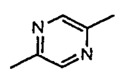
Formula Ic

Y	A
O	
NH	
O	
N-C≡N	
NH	
O	
$\overset{\text{OH}}{\text{N}}$	

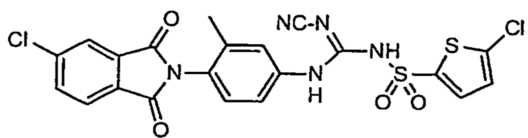
B. Table 4



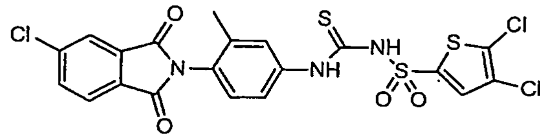
Formula Id

R_1	R_2	W
H		
Me		
		
H		
H		
Me		
H		

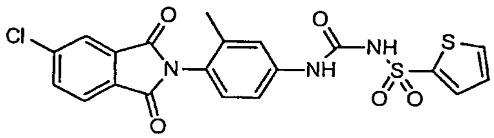
Examples of specific preferred compounds are listed below:



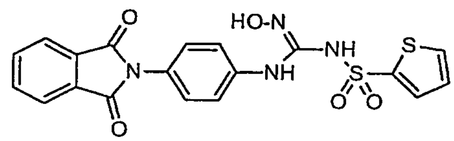
Example 1



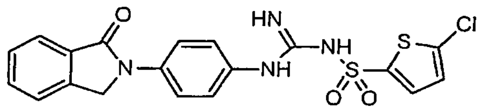
Example 2



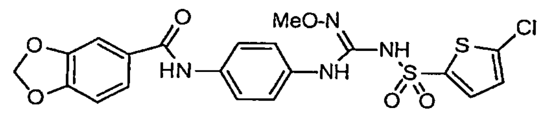
Example 3



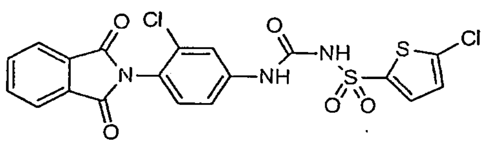
Example 4



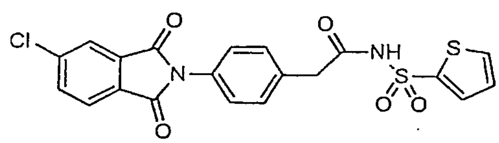
Example 5



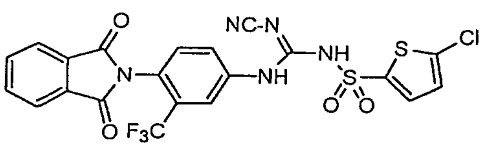
Example 6



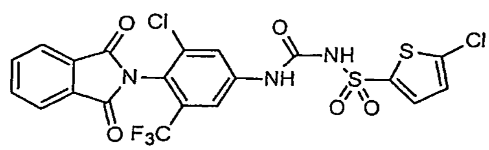
Example 7



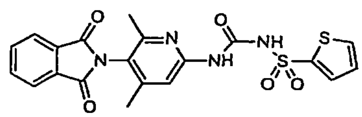
Example 8



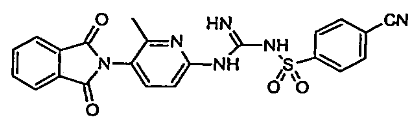
Example 9



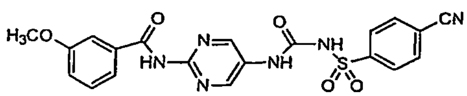
Example 10



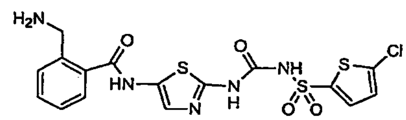
Example 11



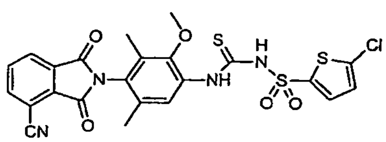
Example 12



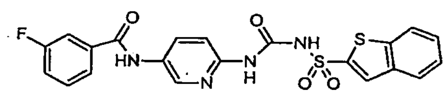
Example 13



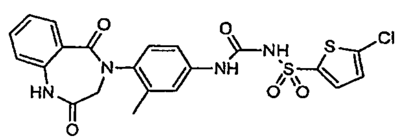
Example 14



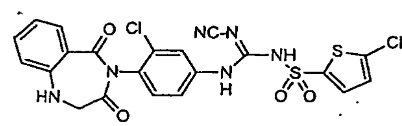
Example 15



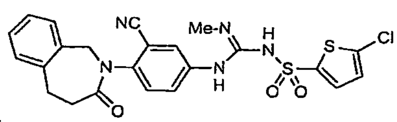
Example 16



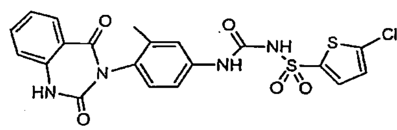
Example 17



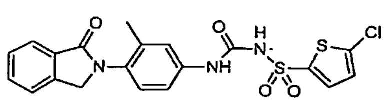
Example 18



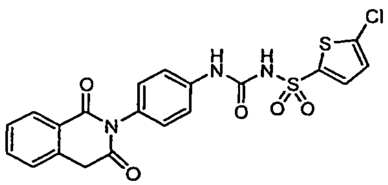
Example 19



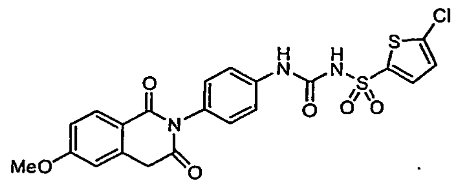
Example 20



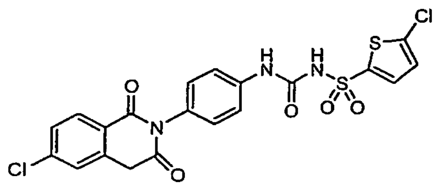
Example 21



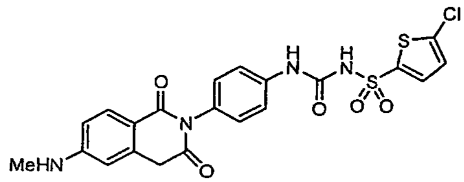
Example 22



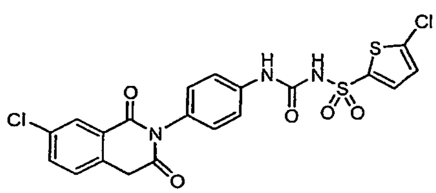
Example 23



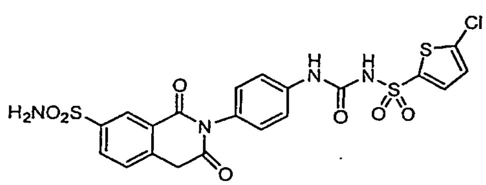
Example 24



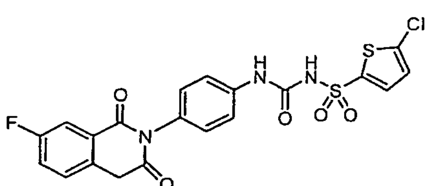
Example 25



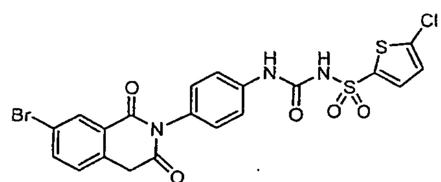
Example 26



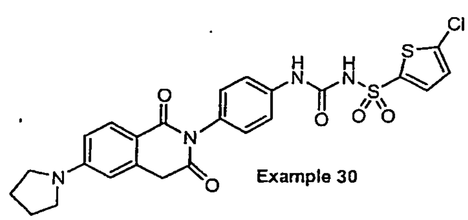
Example 27



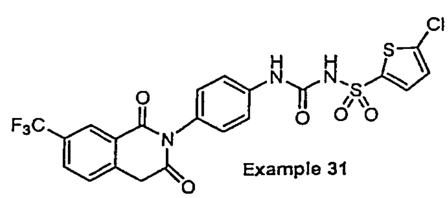
Example 28



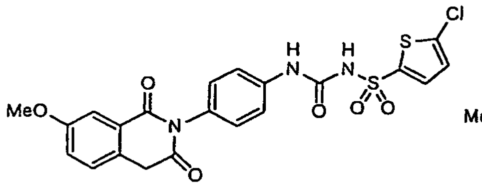
Example 29



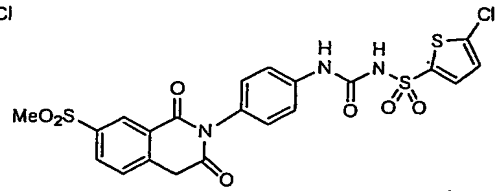
Example 30



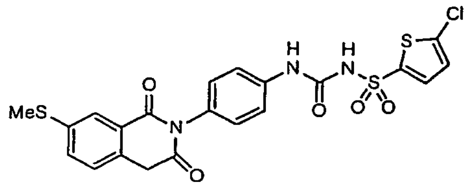
Example 31



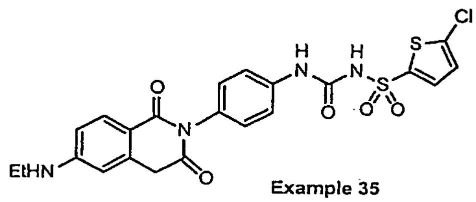
Example 32



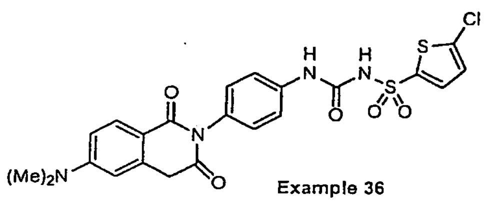
Example 33



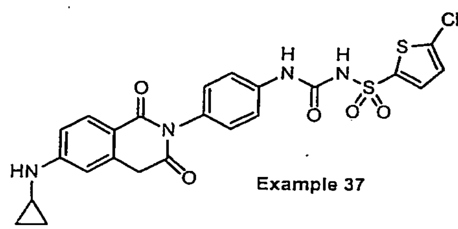
Example 34



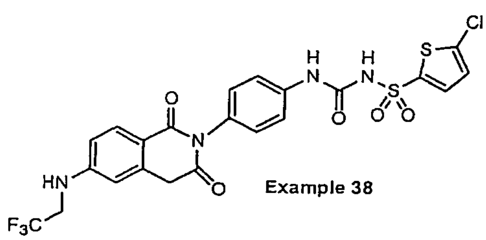
Example 35



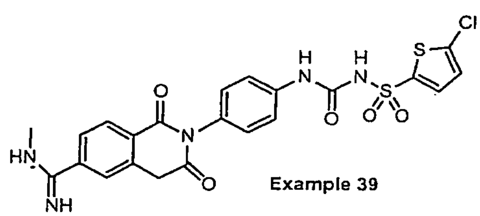
Example 36



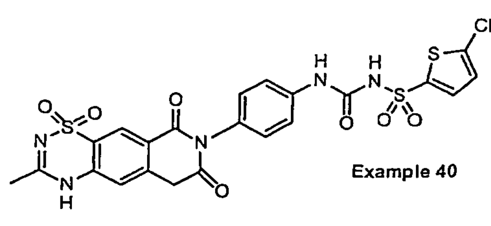
Example 37



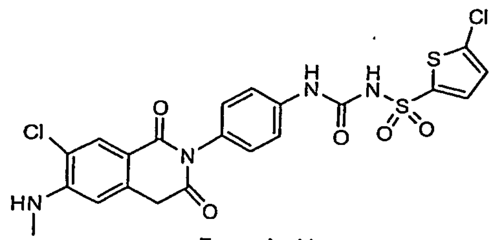
Example 38



Example 39



Example 40



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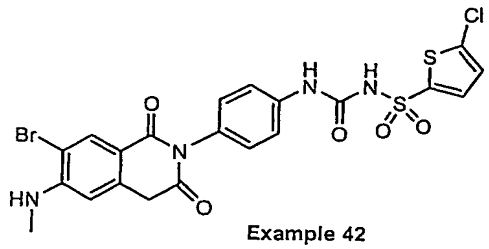

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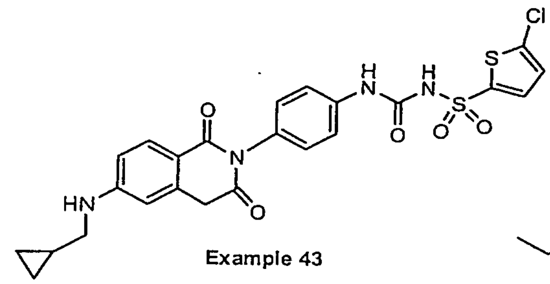

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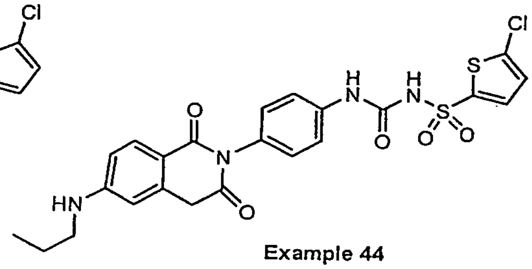

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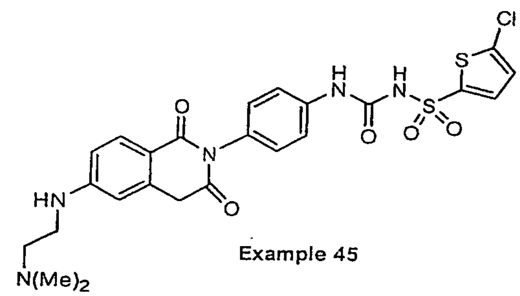

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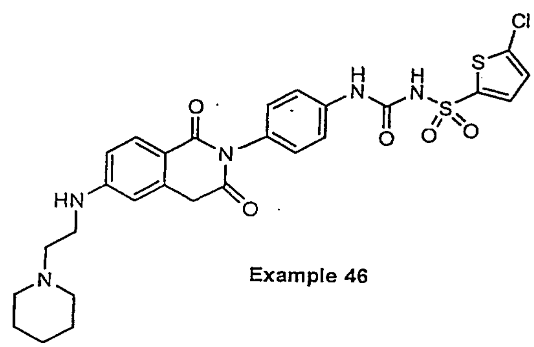

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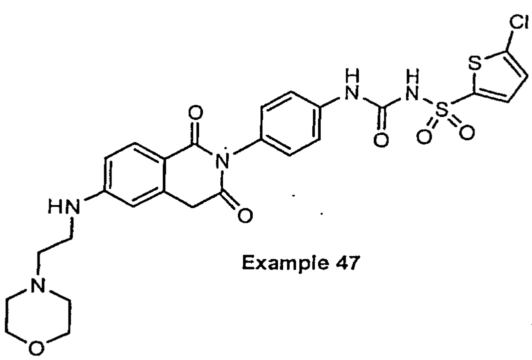

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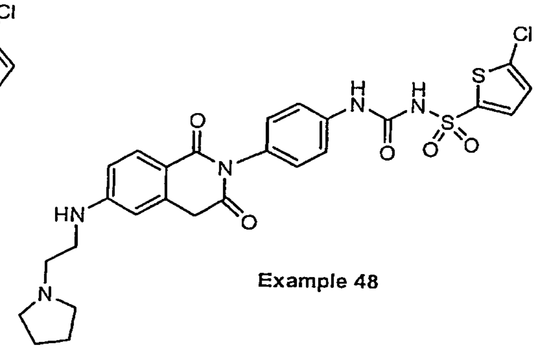
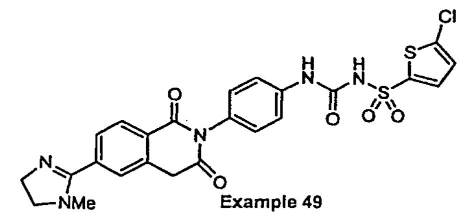
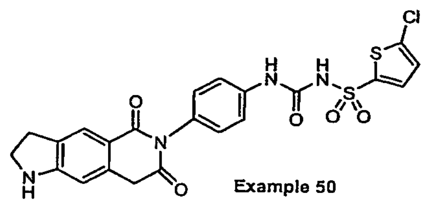


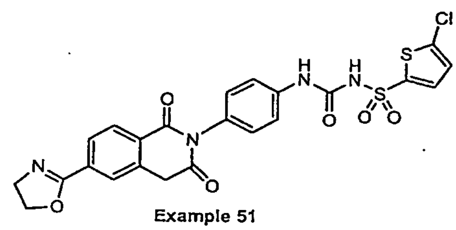
Example 48



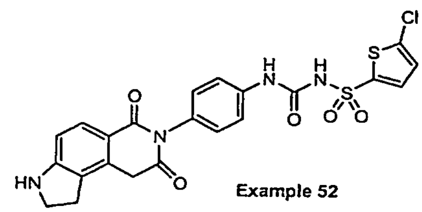
Example 49



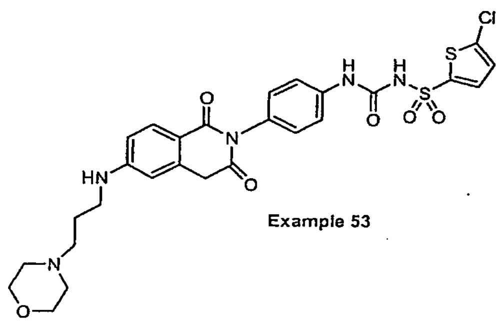
Example 50



Example 51



Example 52



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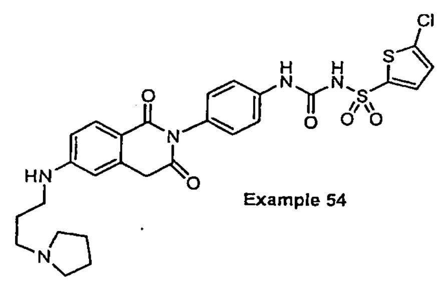
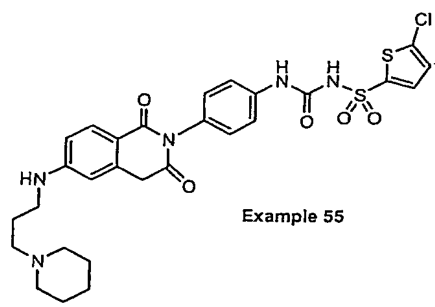
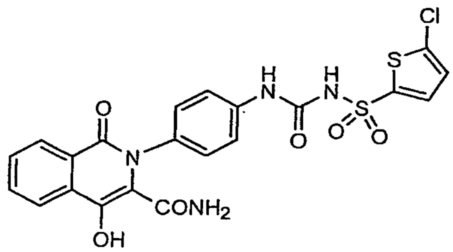


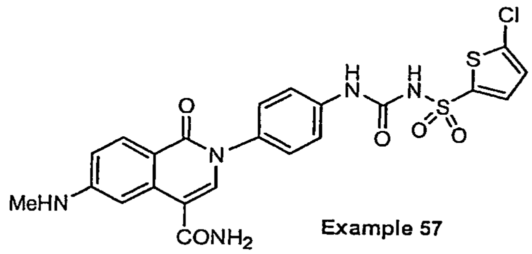
Example 54



Example 55



Example 56



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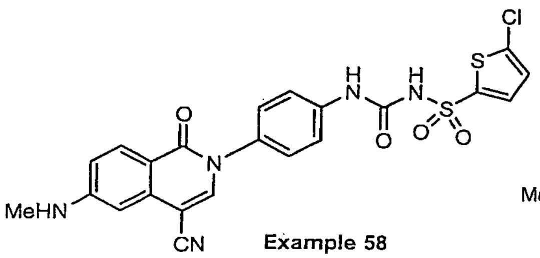
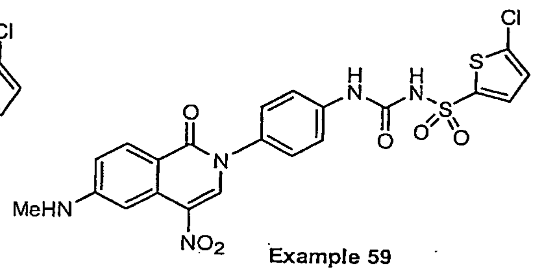
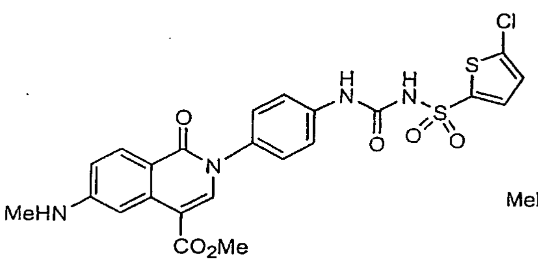


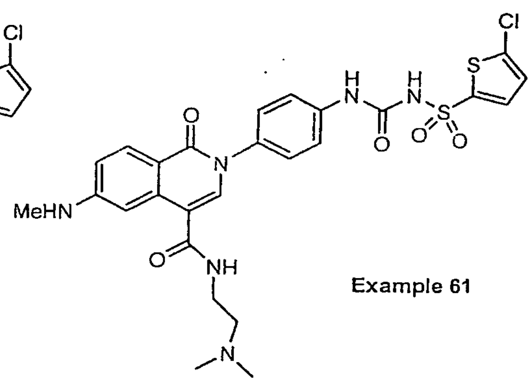
Example 58



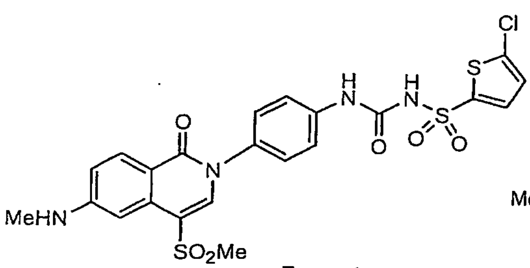
Example 59



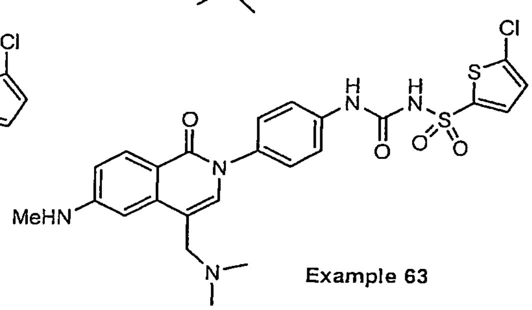
Example 60



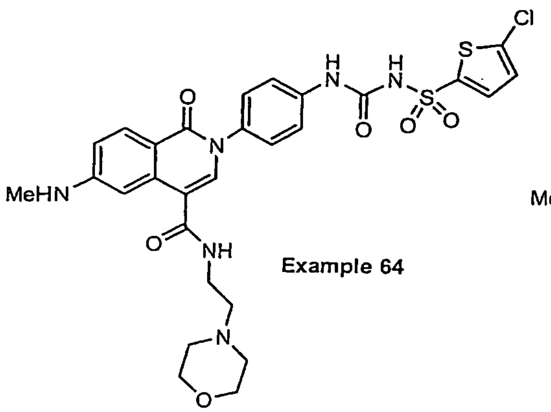
Example 61



Example 62



Example 63



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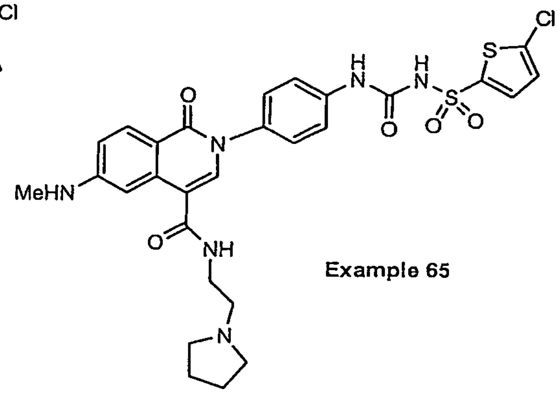
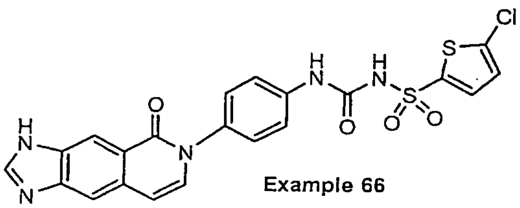


Example 65



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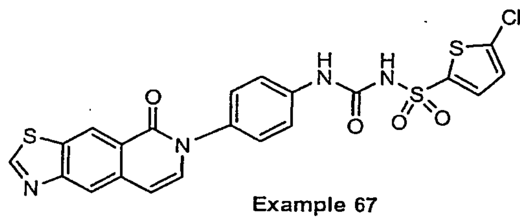

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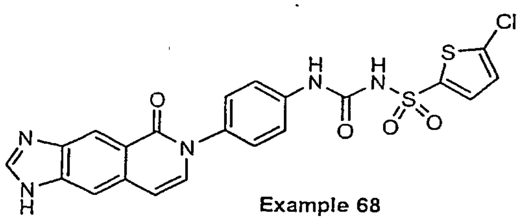
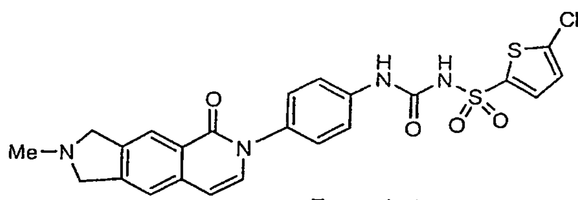
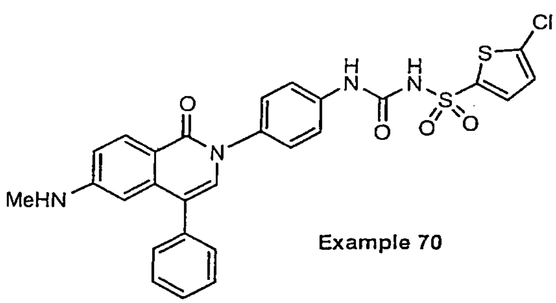


Example 68



Example 69



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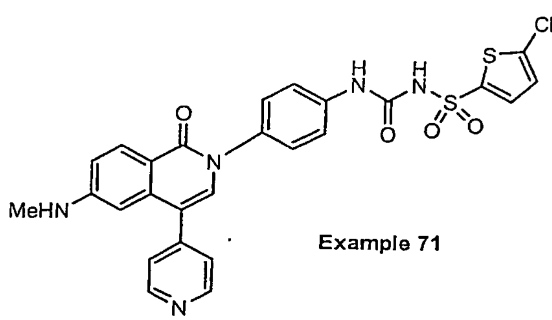

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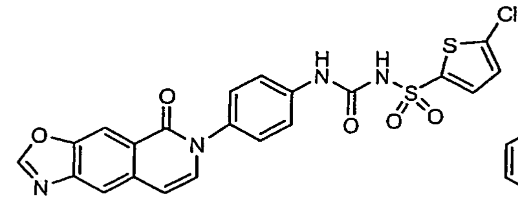

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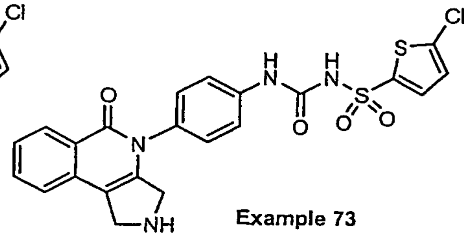

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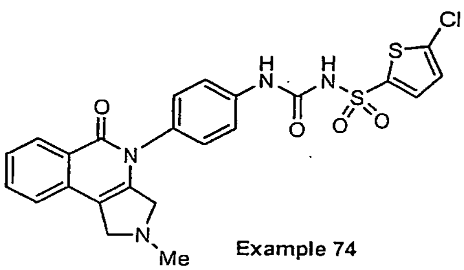

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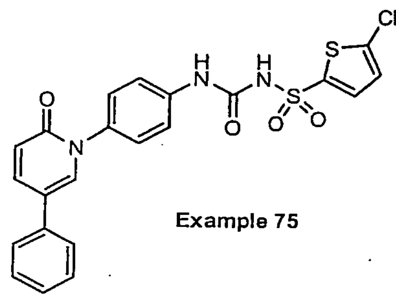

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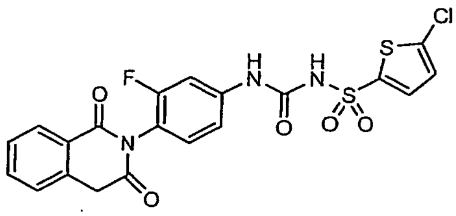

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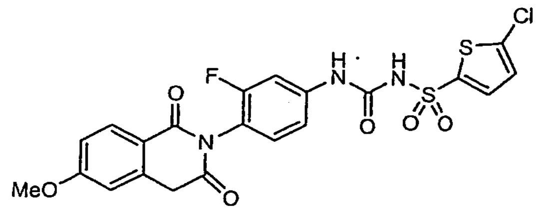

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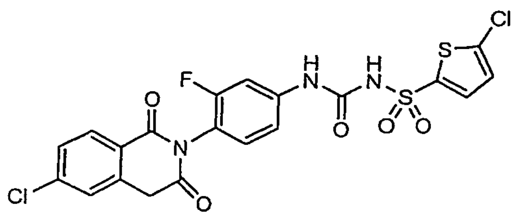

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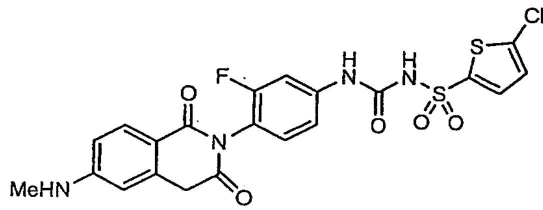

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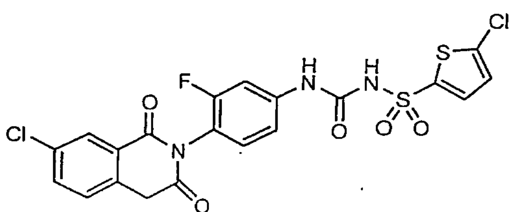

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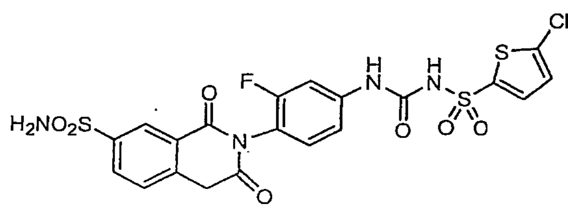

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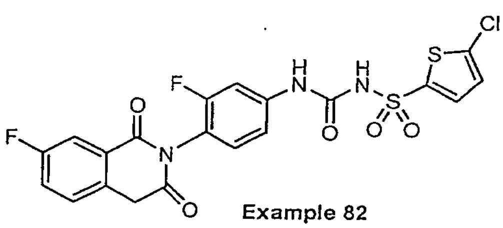

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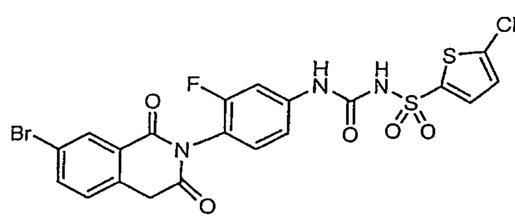

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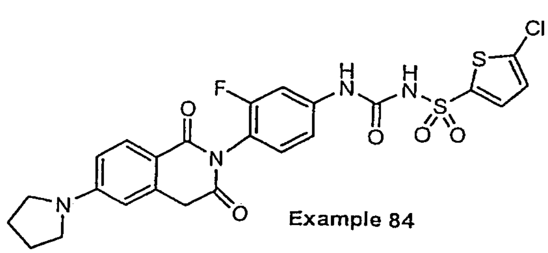

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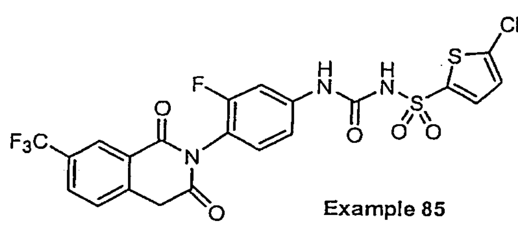

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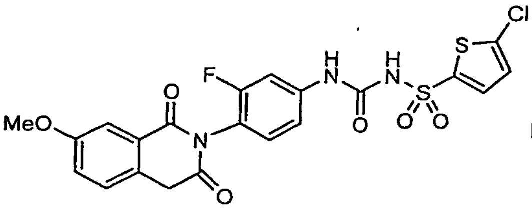

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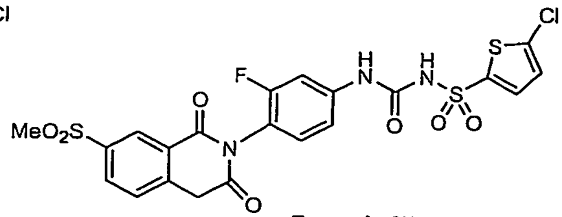

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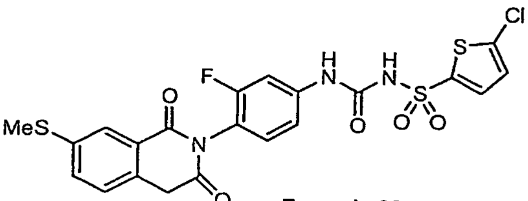

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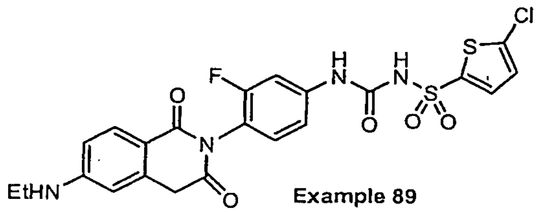

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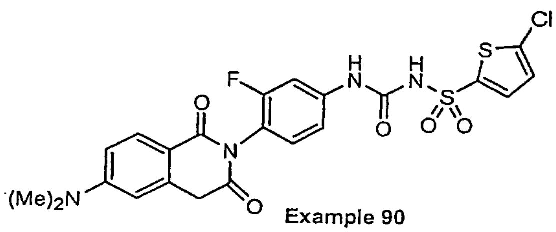

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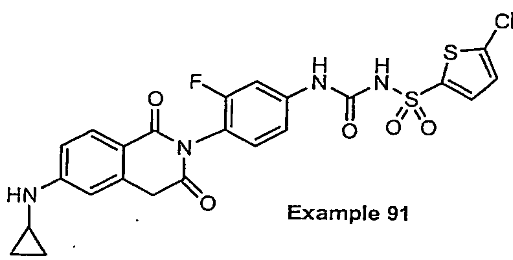

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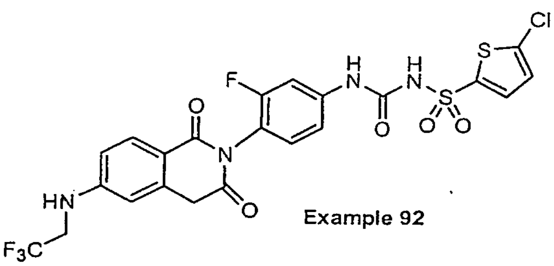

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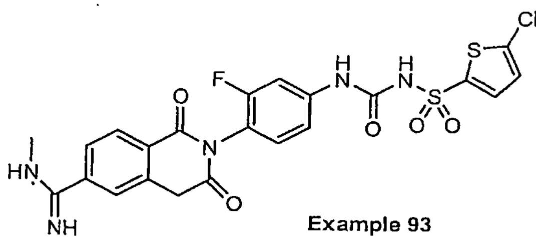

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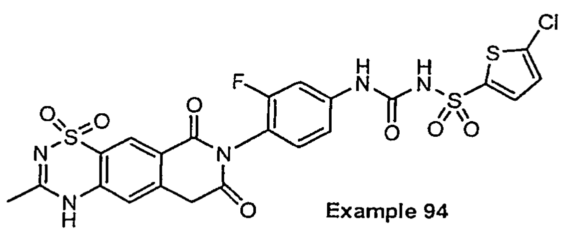

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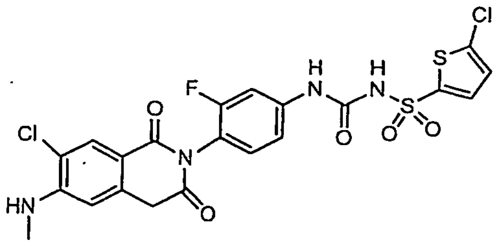

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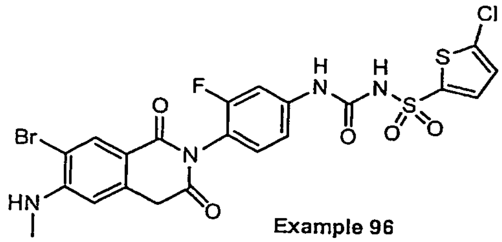

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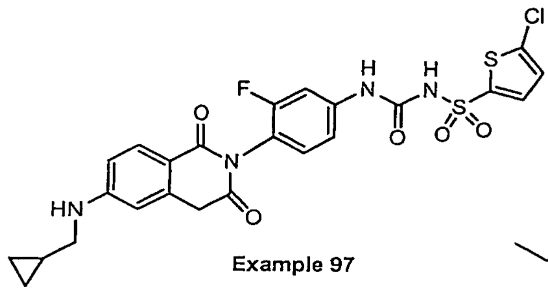

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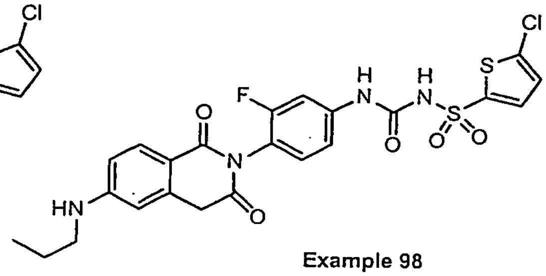

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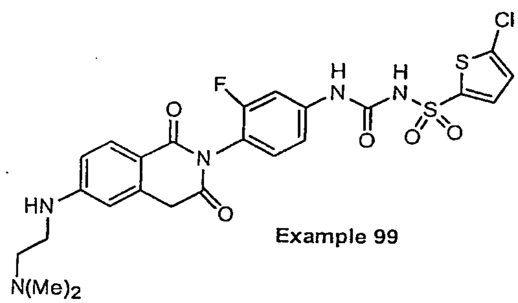

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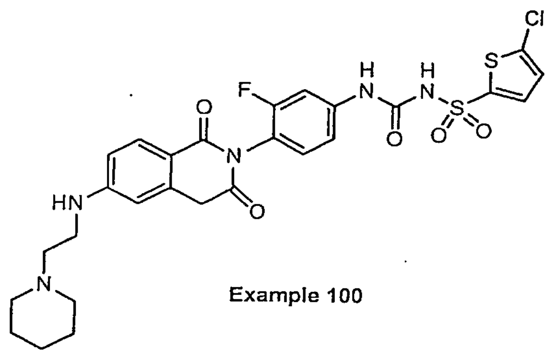

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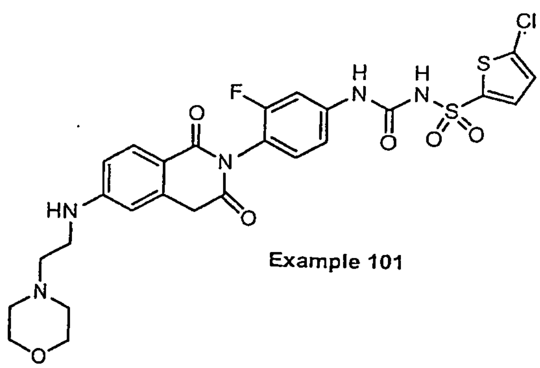

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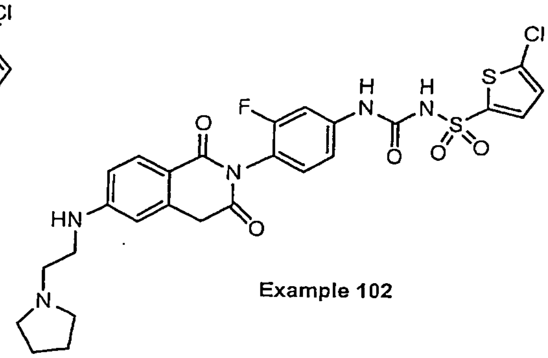

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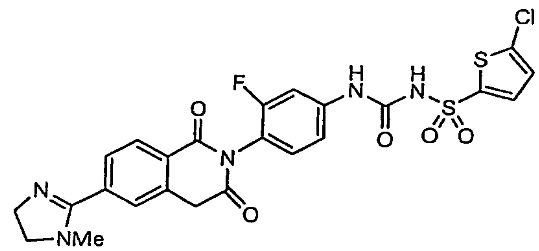

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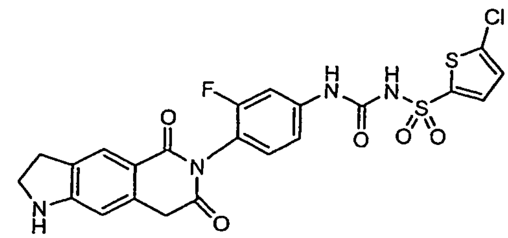

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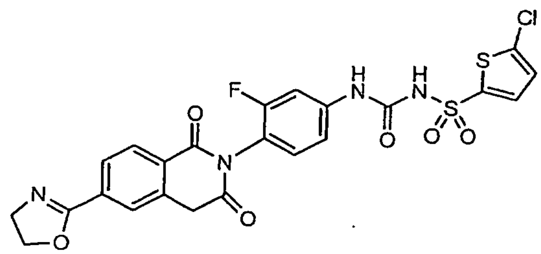

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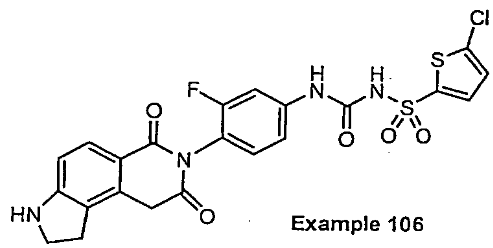

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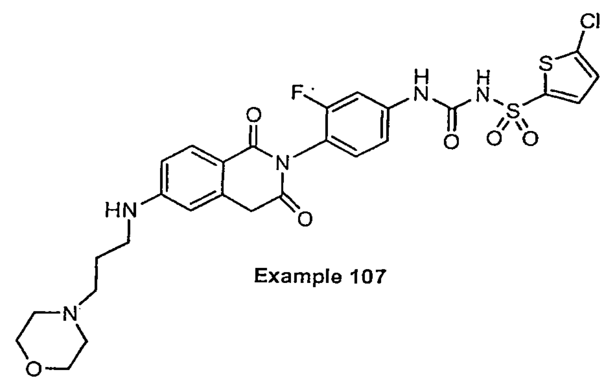

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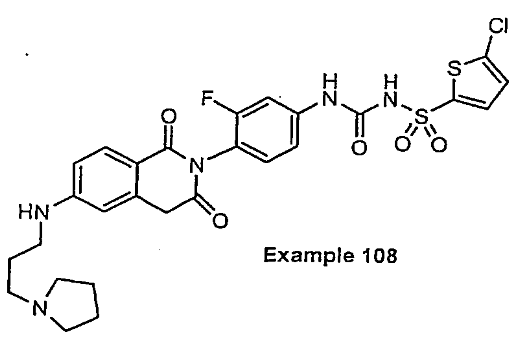

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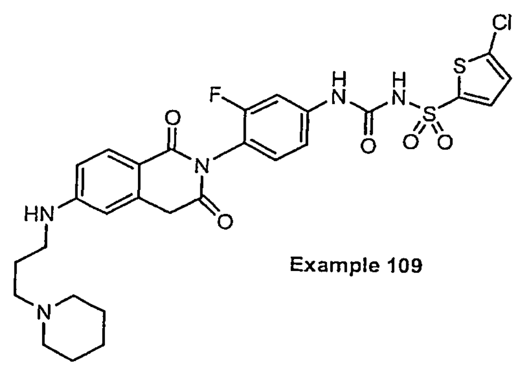

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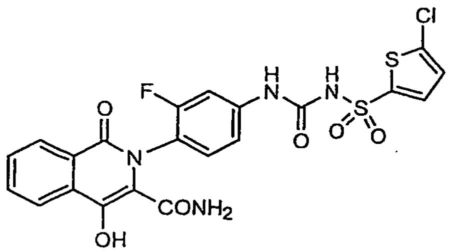

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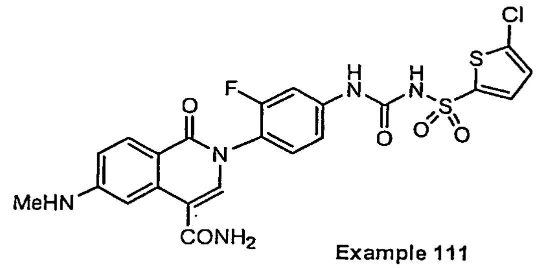

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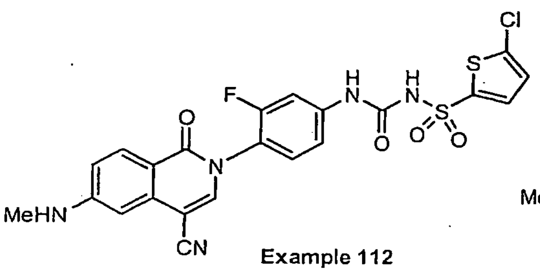

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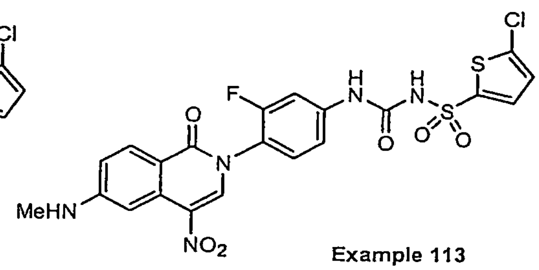

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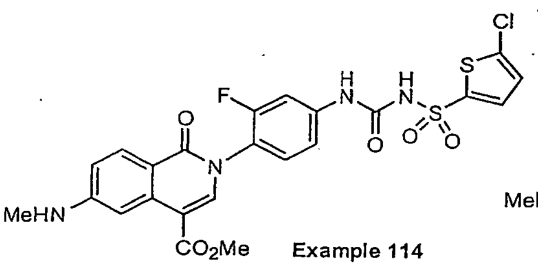

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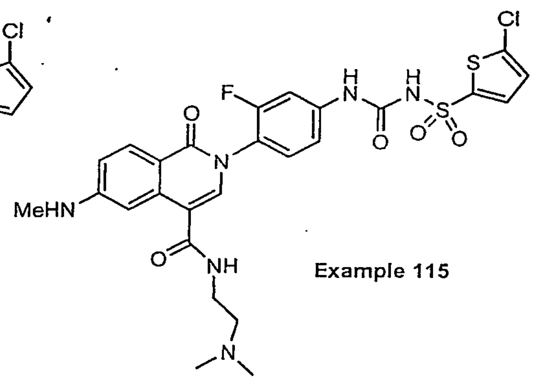

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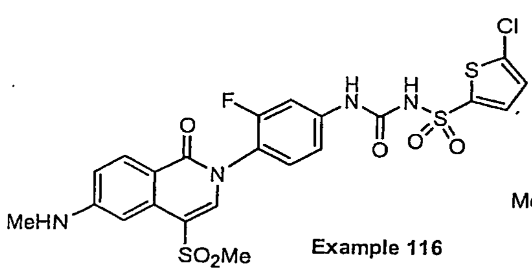

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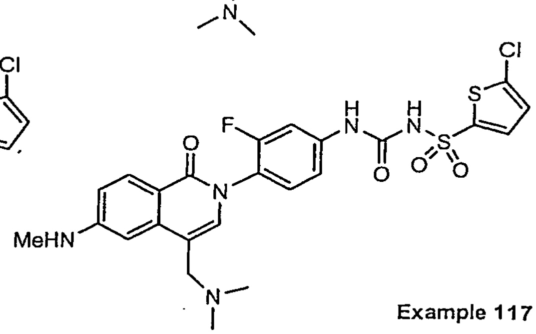

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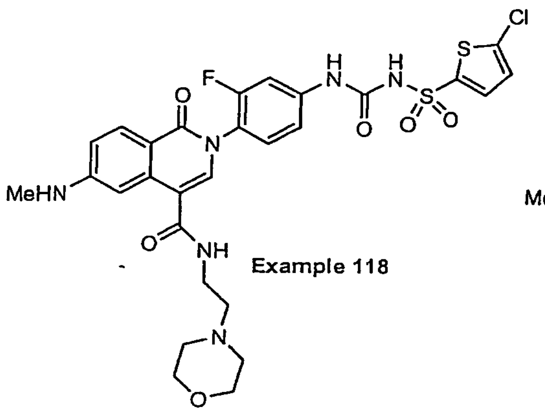

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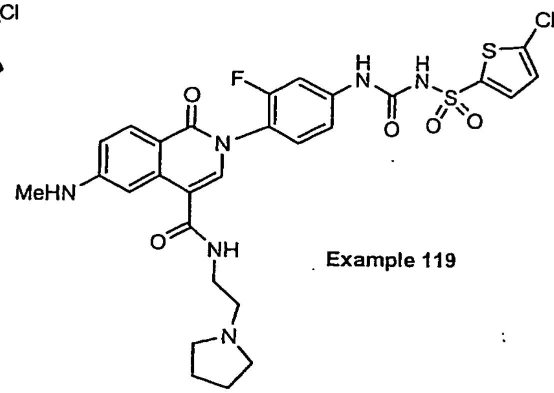

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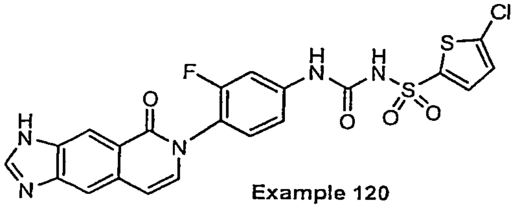

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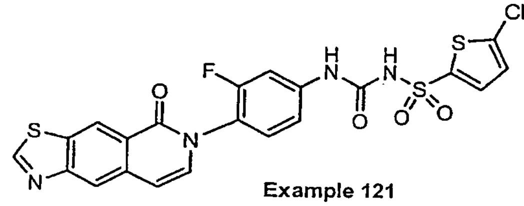

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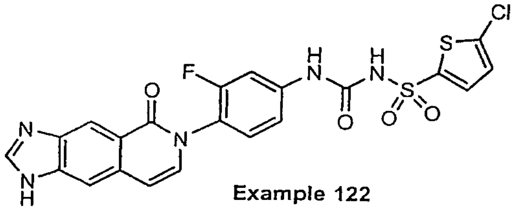

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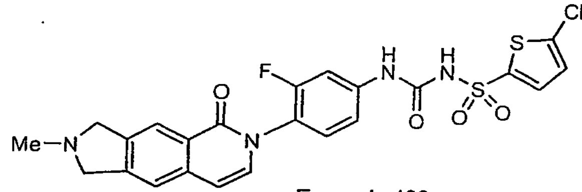

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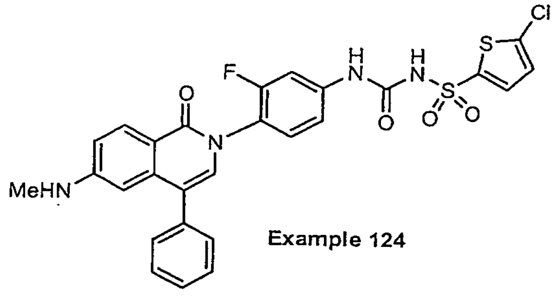

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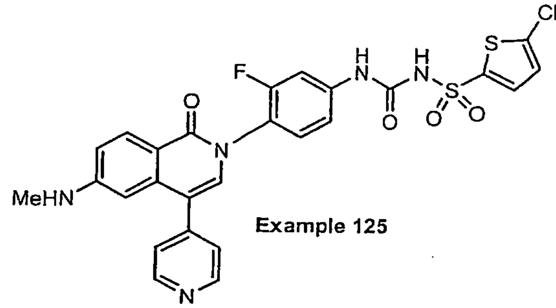

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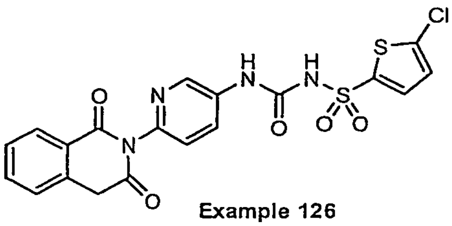

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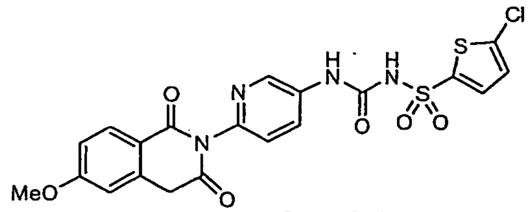

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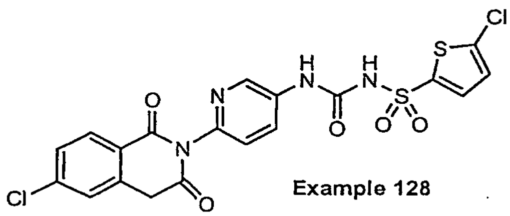

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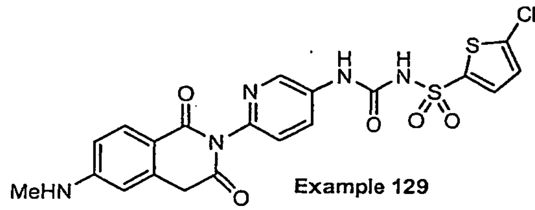

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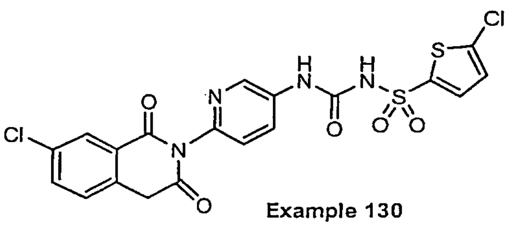

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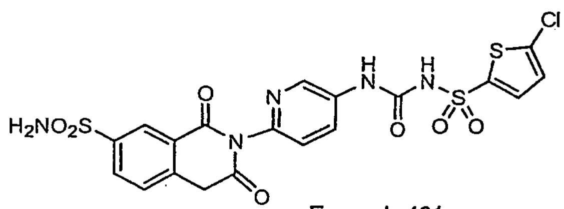

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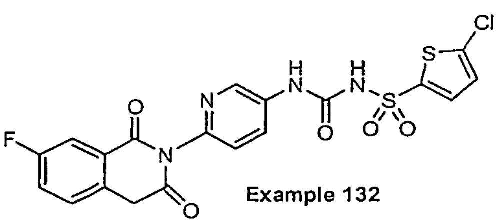

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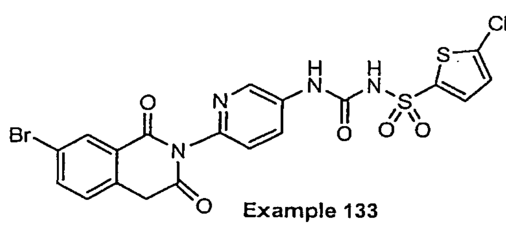

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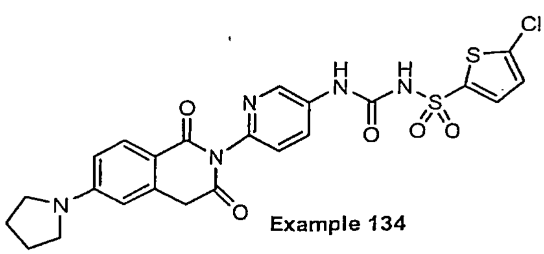

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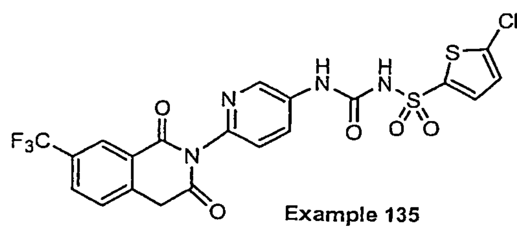

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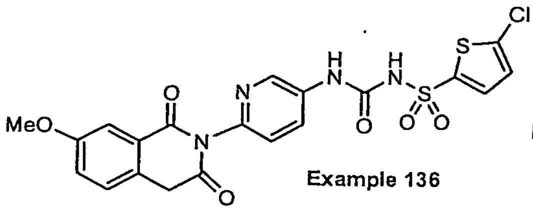

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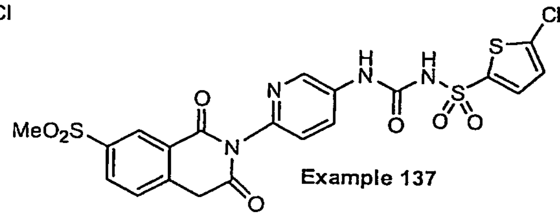

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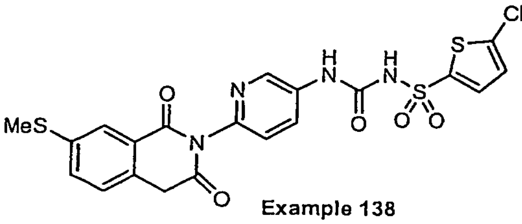

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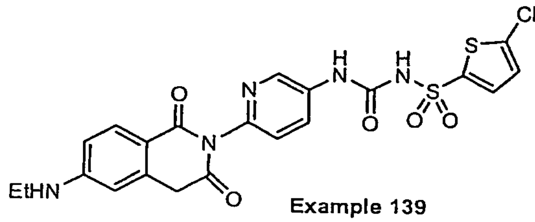

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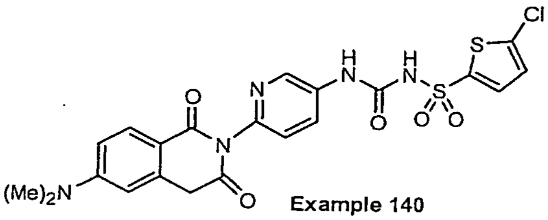

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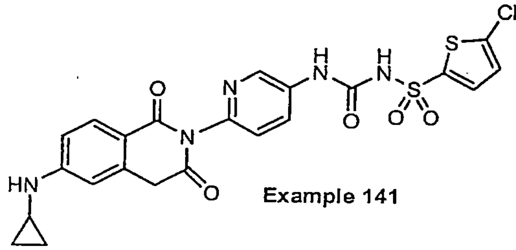

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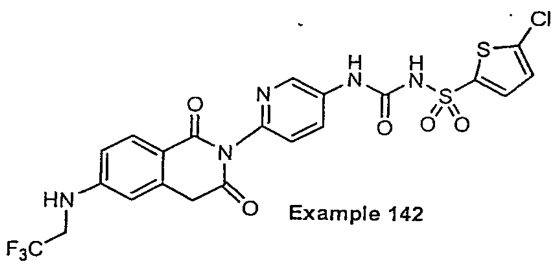

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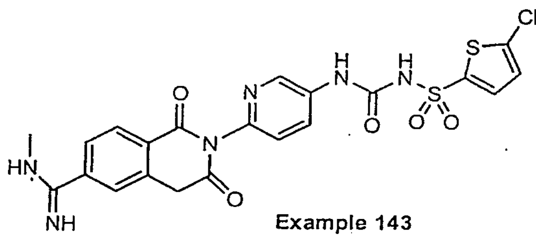
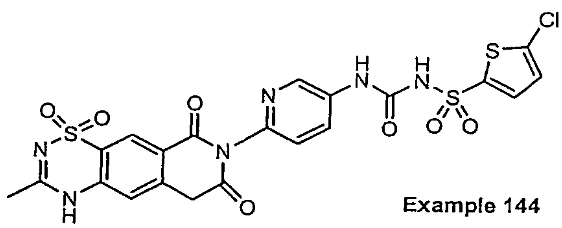


Example 143



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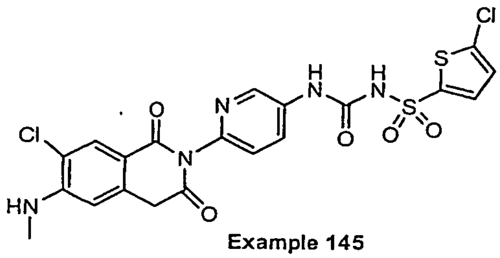

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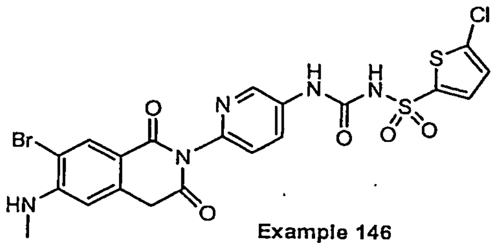

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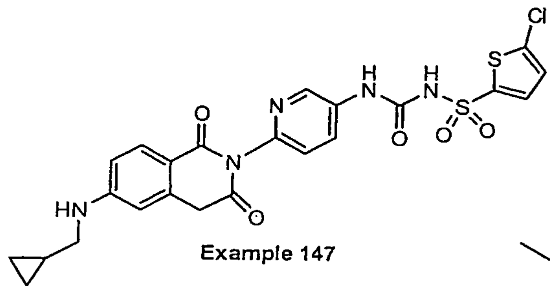

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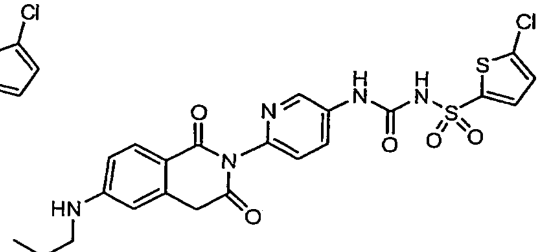

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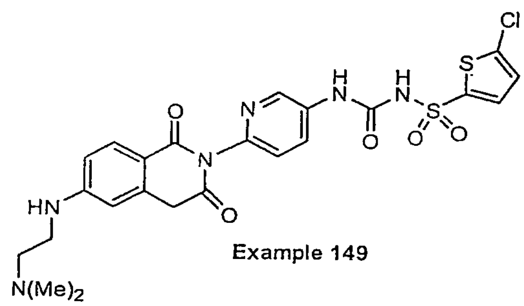

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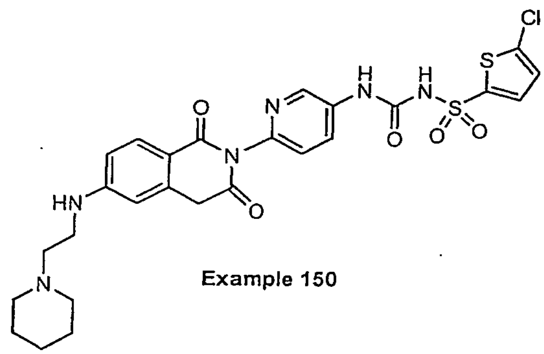

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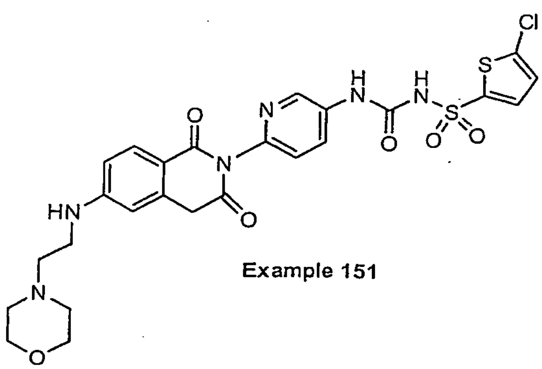

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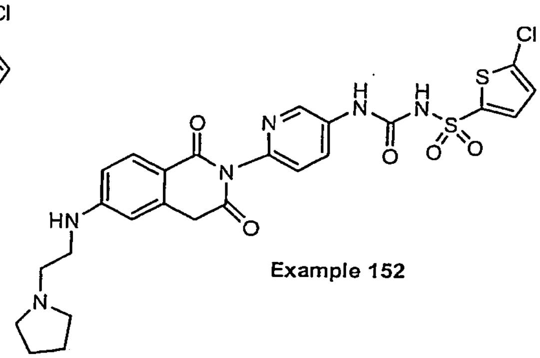

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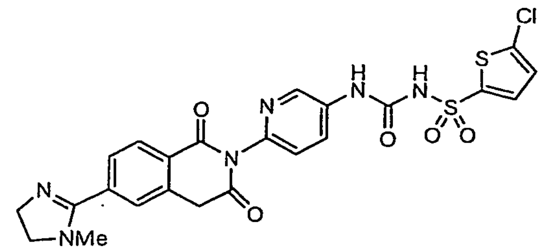

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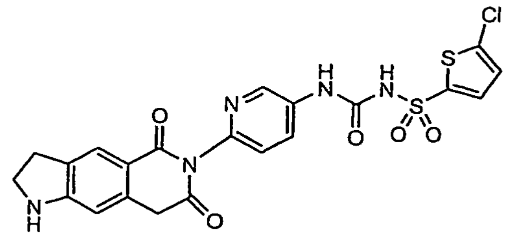

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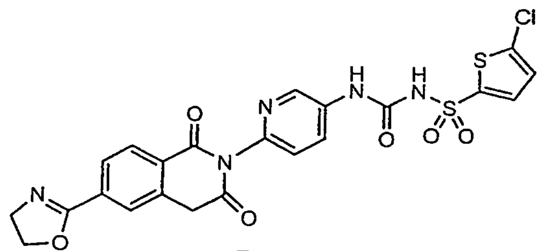

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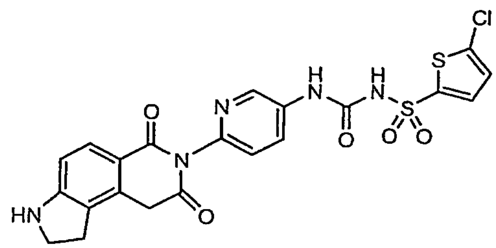

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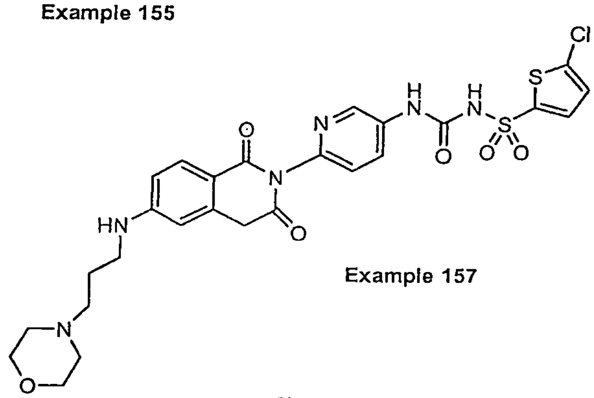

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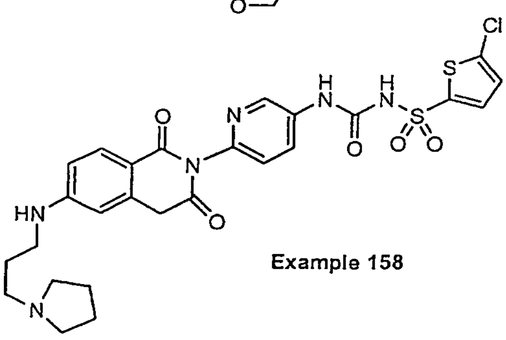

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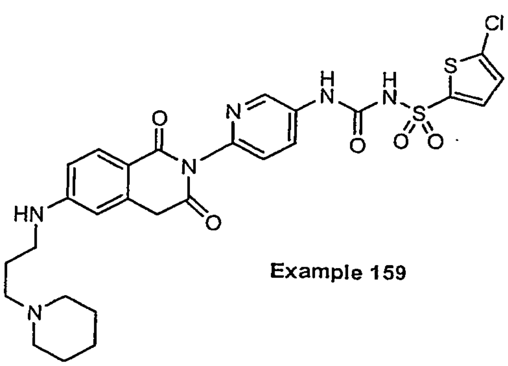

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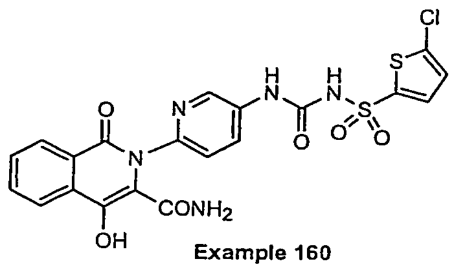

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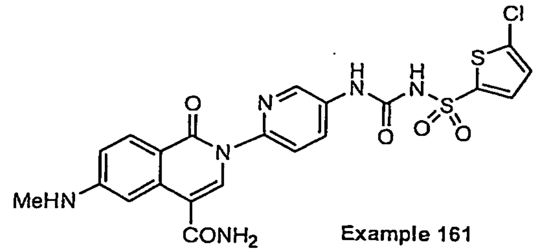

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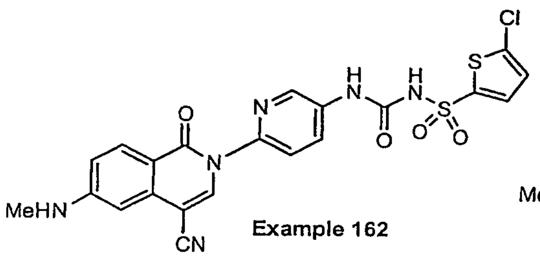

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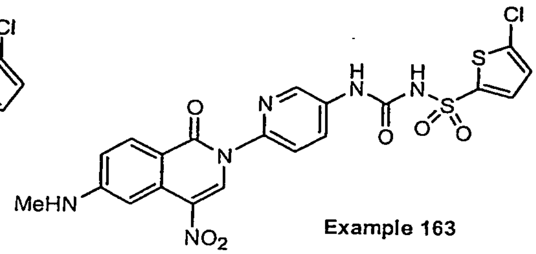

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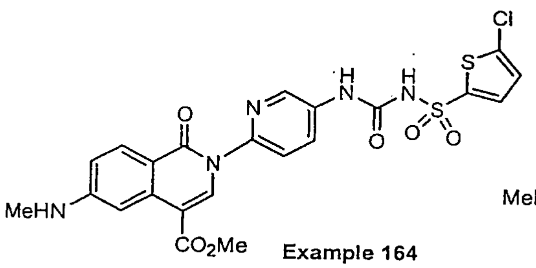

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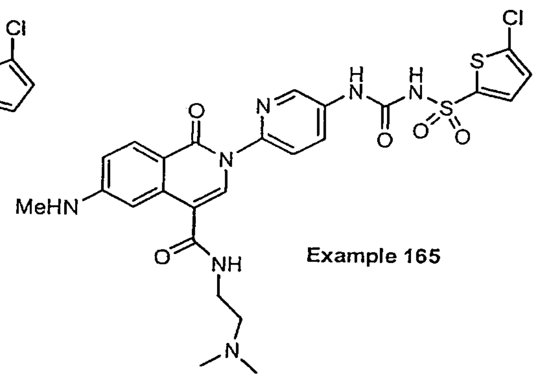

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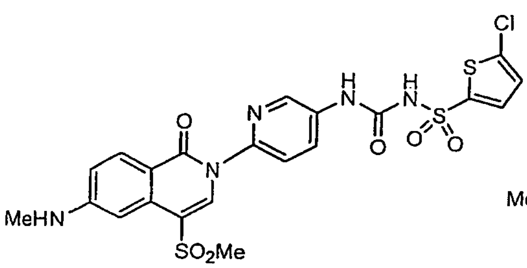

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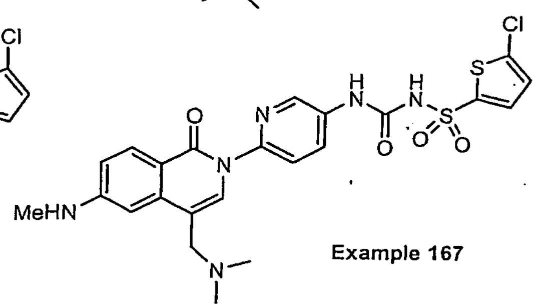

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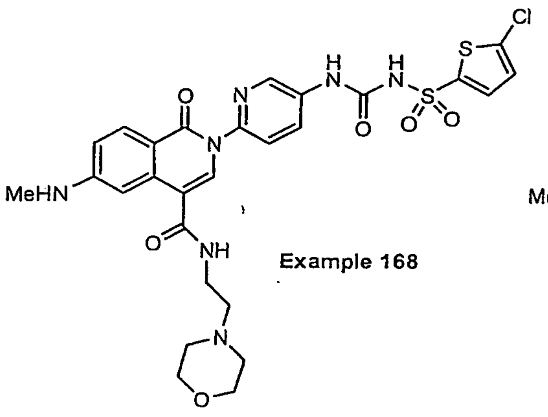

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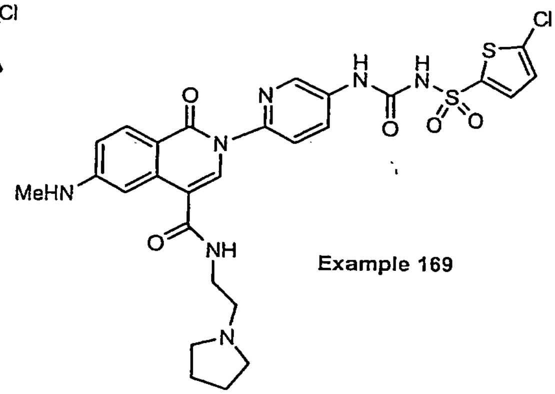

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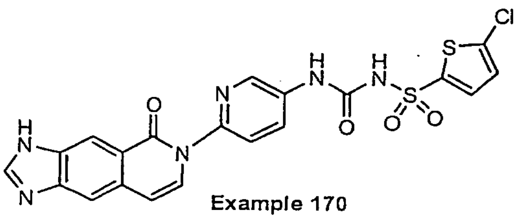

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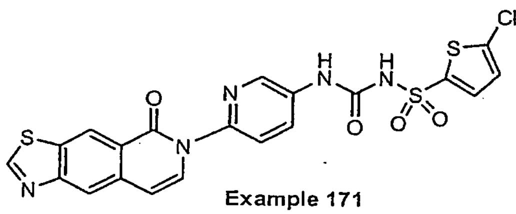

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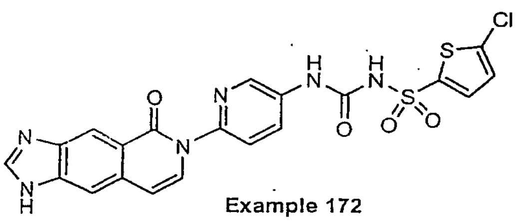

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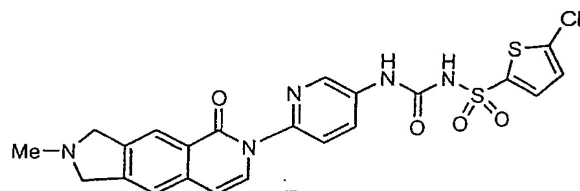

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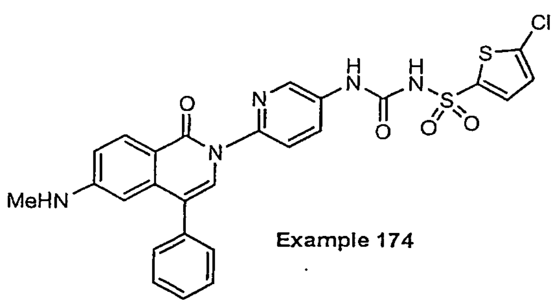

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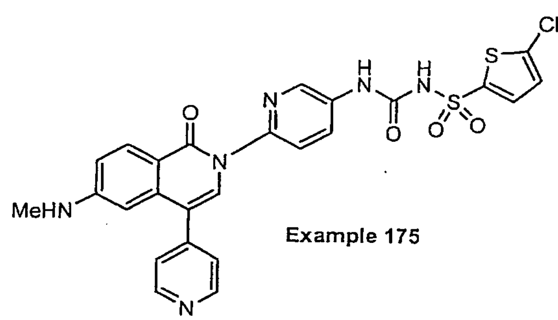

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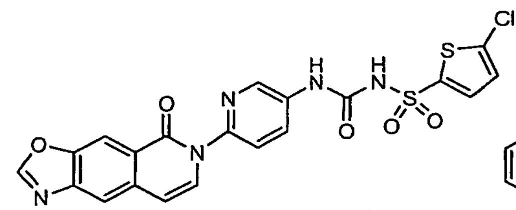

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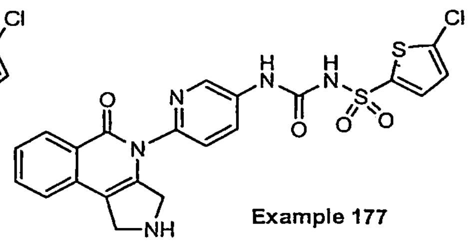

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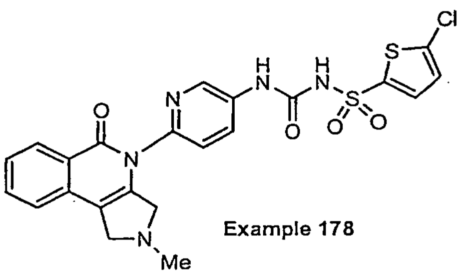

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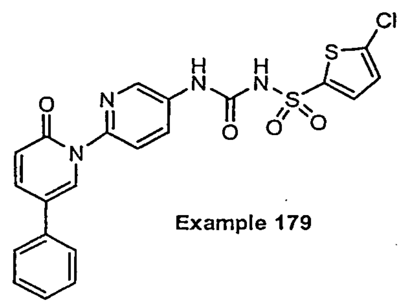

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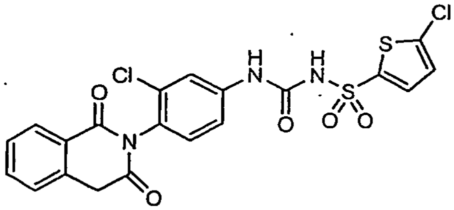

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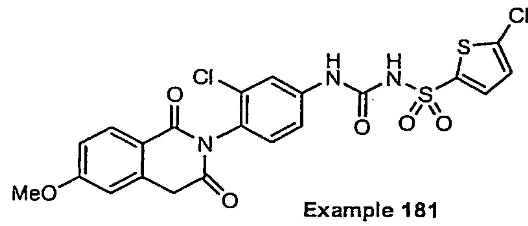

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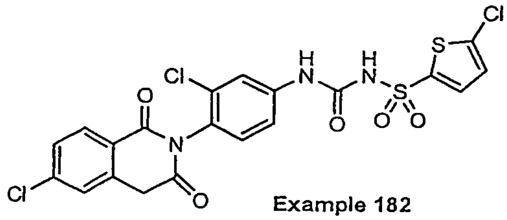

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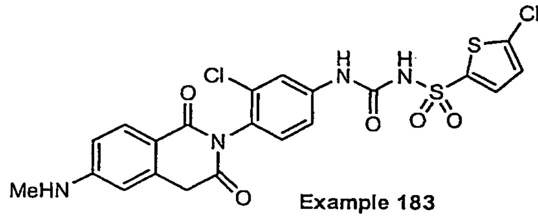

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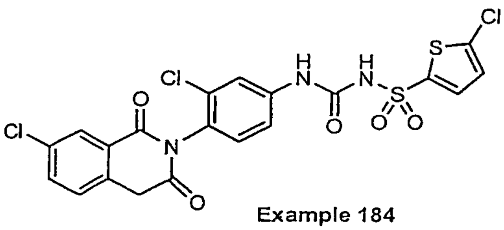

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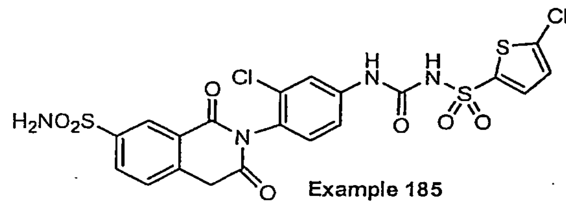

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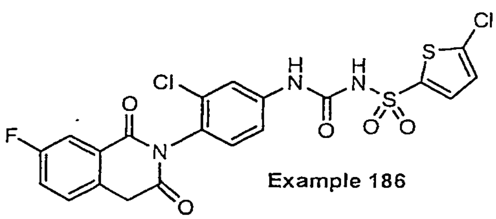

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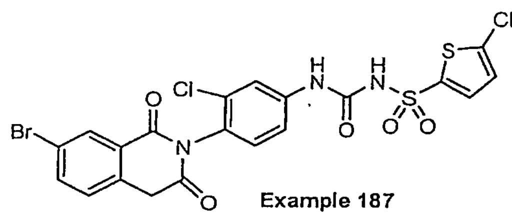

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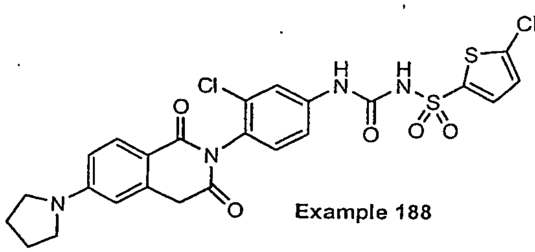

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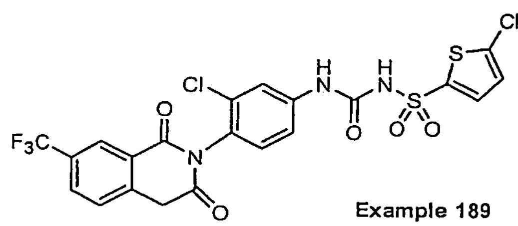

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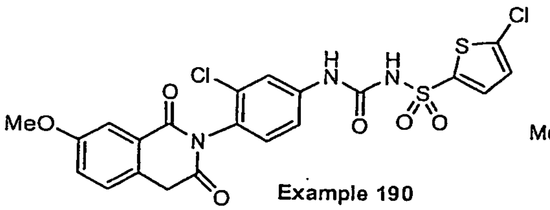

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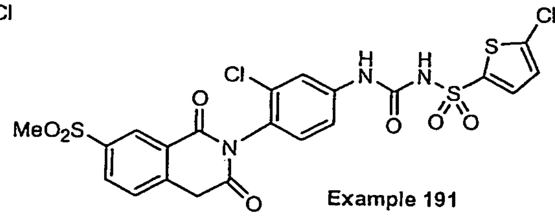

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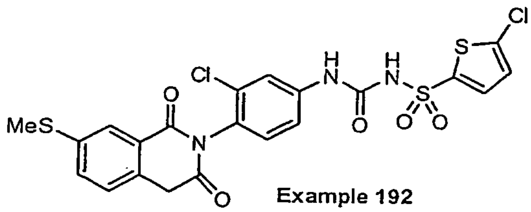

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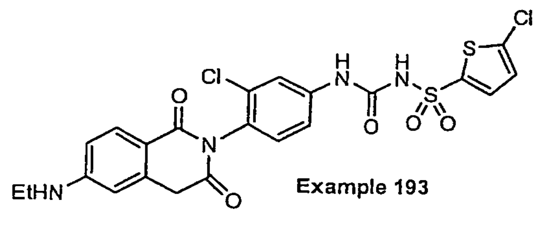

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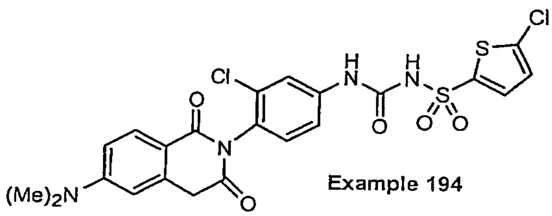

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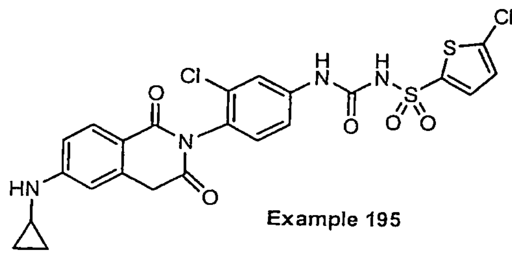

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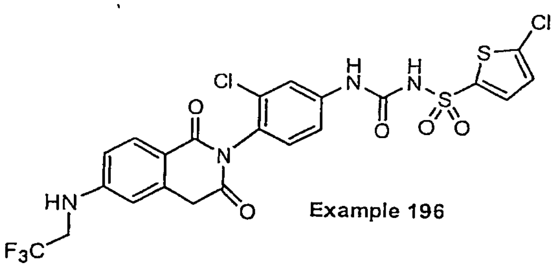

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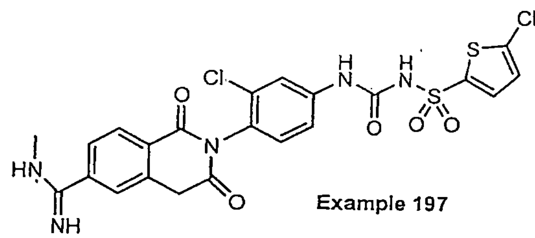

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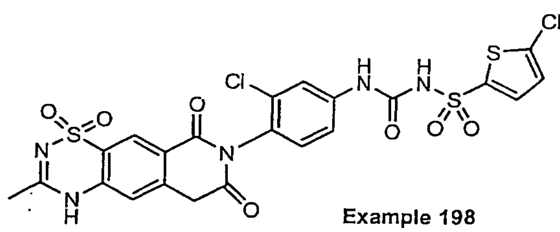

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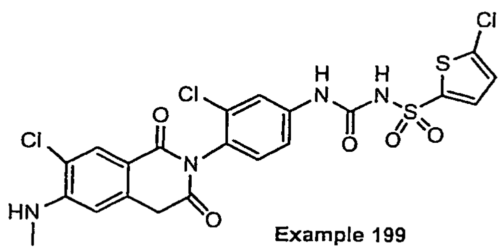
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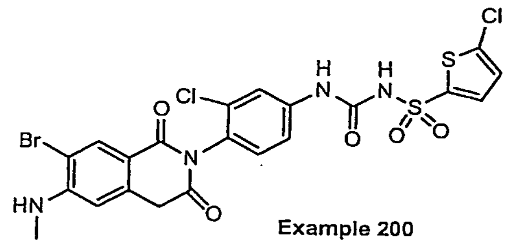
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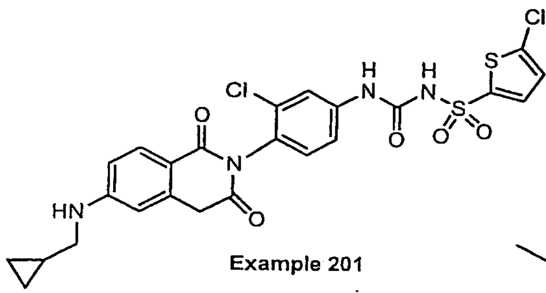
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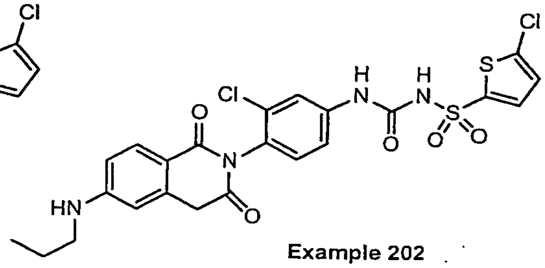
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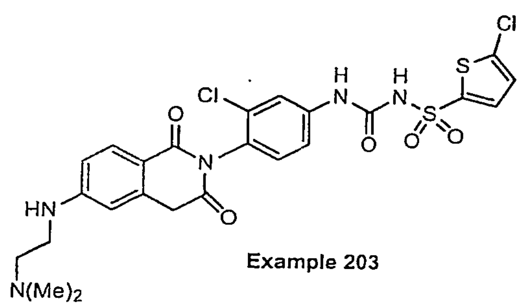
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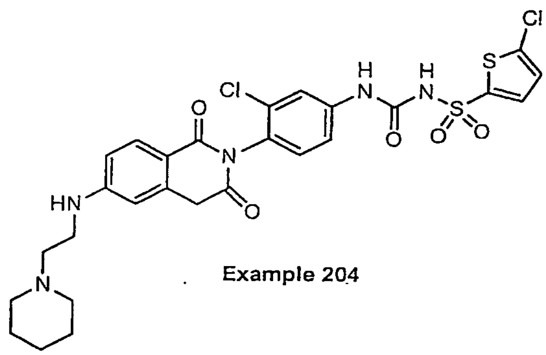
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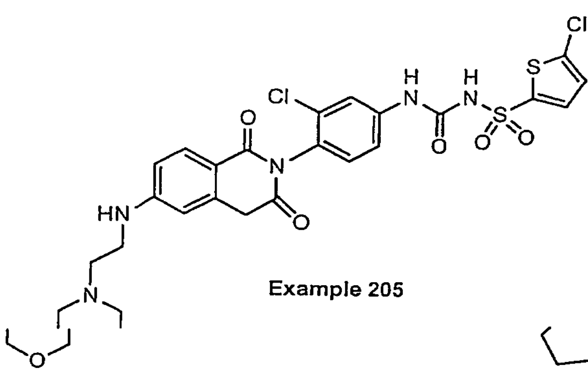
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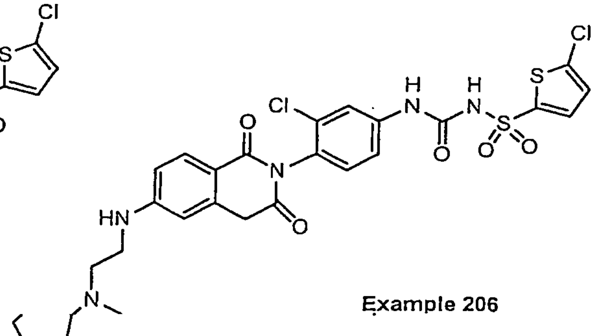
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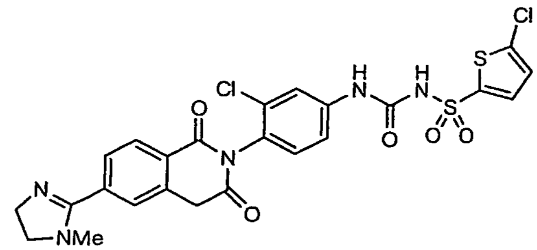

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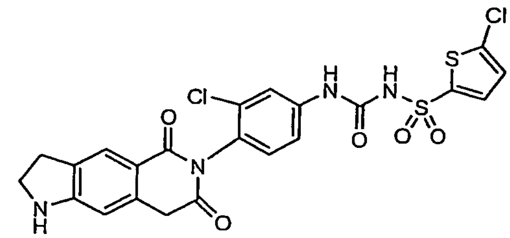

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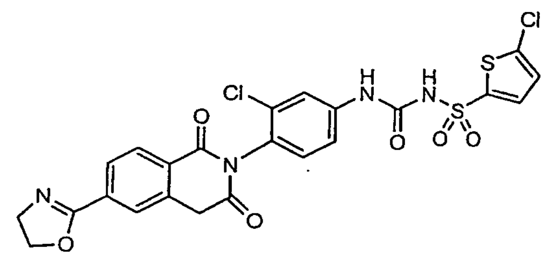

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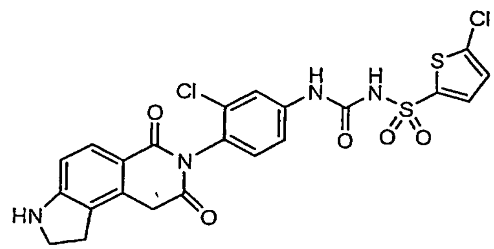

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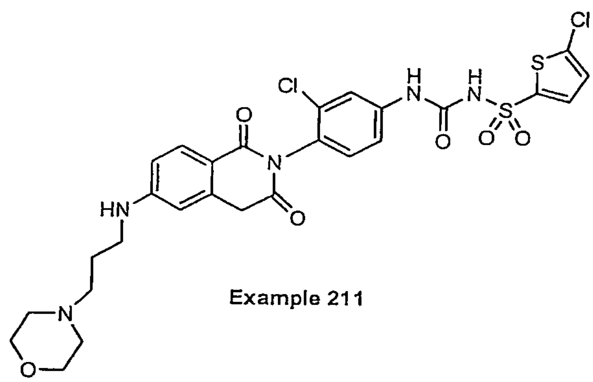

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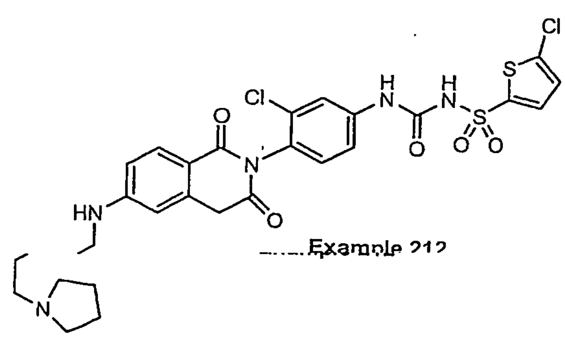

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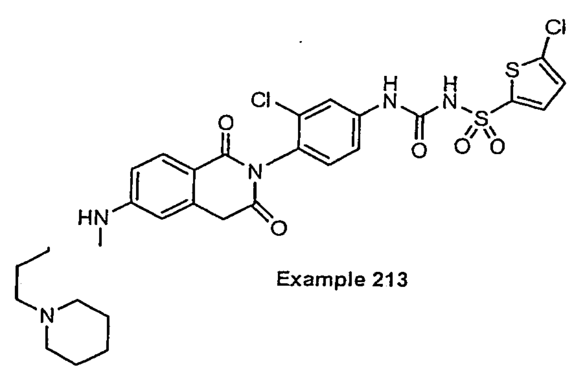

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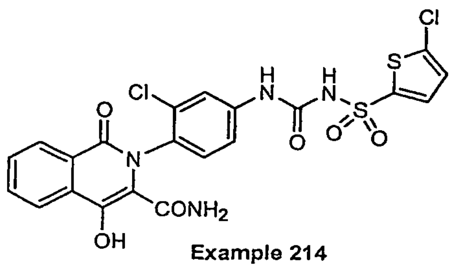

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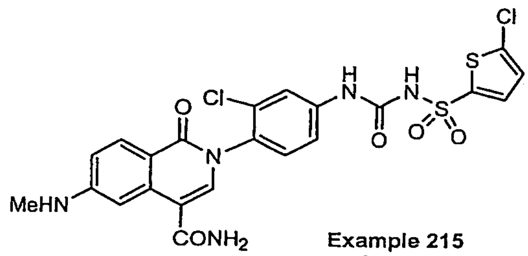

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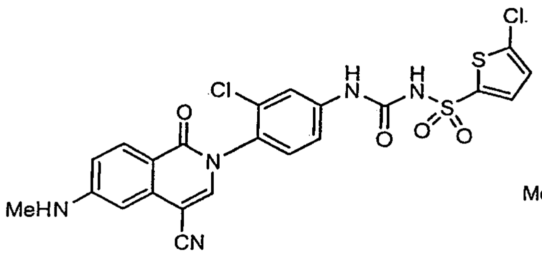

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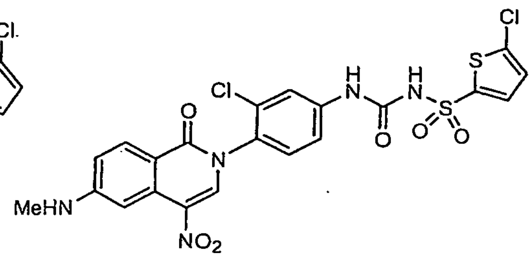
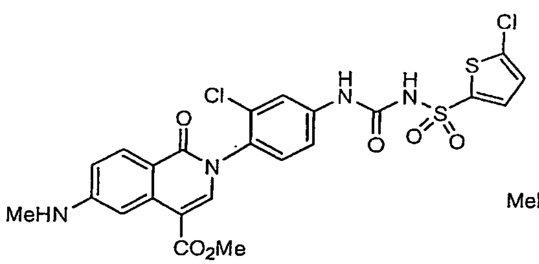


Example 217



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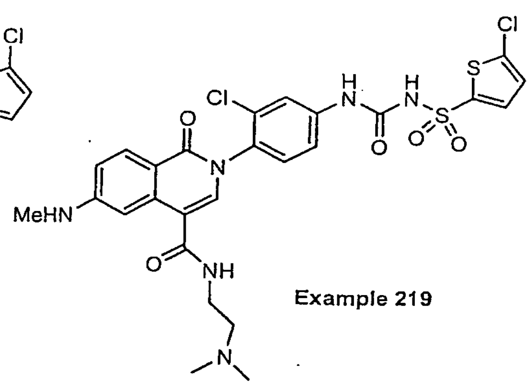

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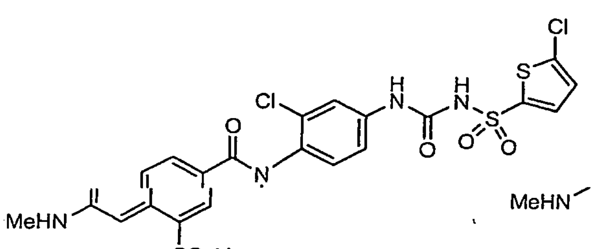

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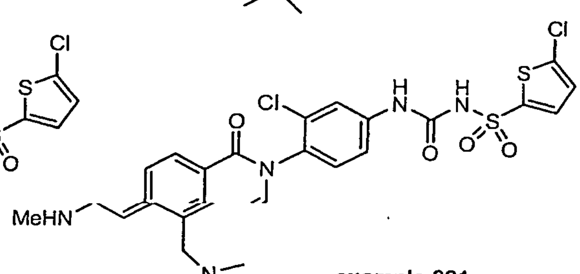

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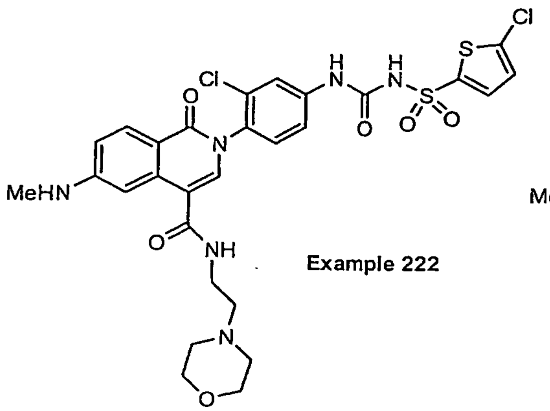

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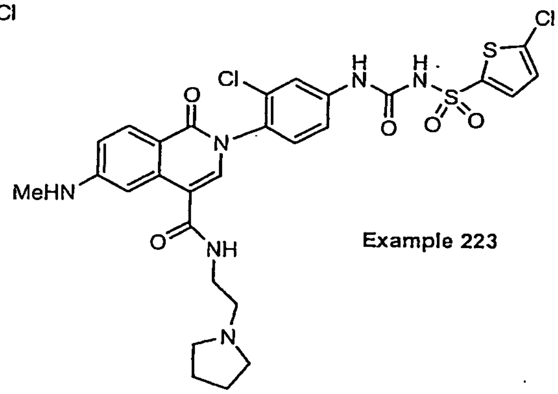

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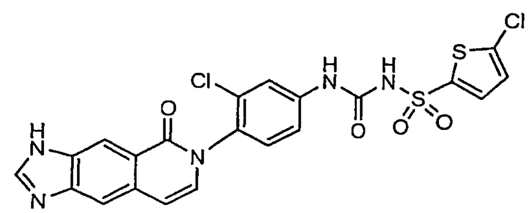

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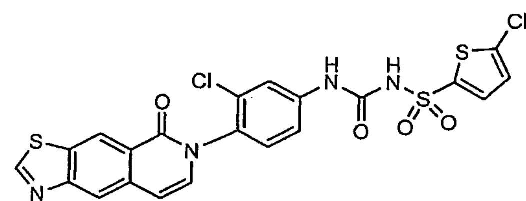

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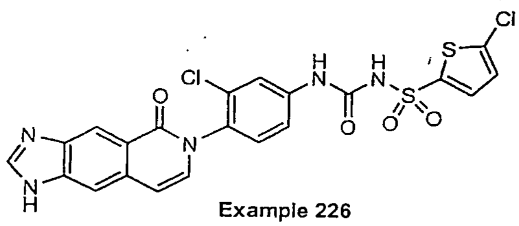

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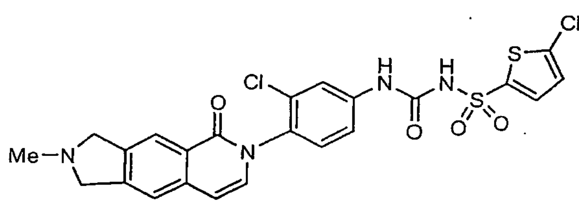

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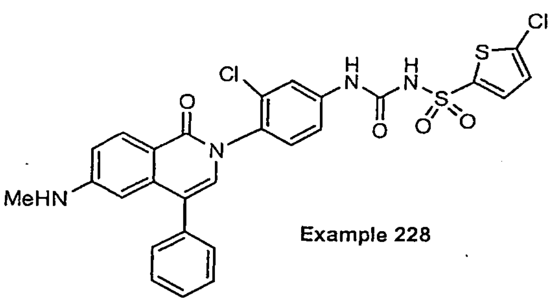

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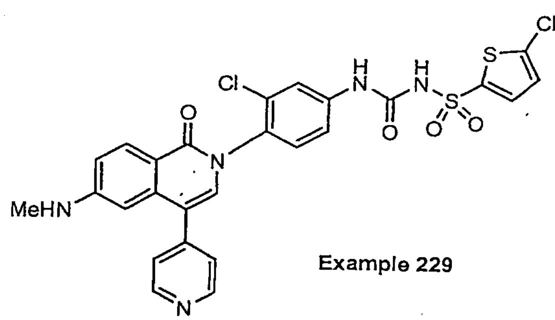

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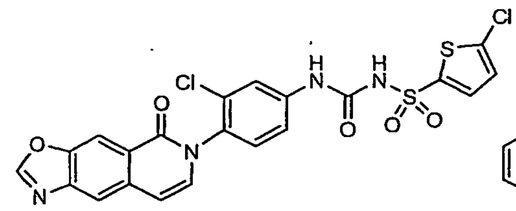

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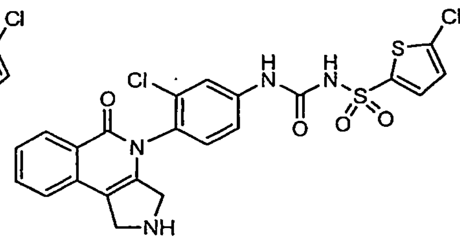

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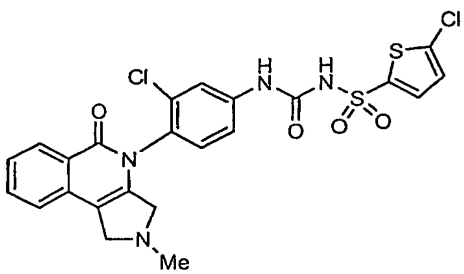

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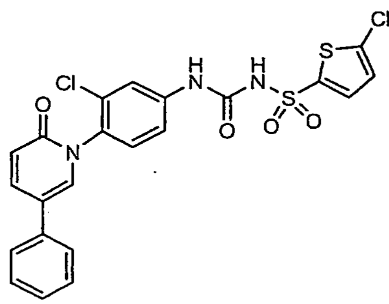

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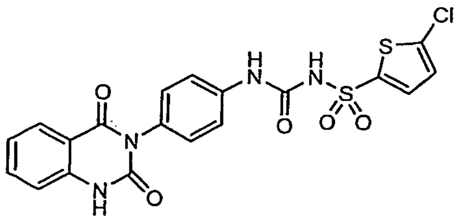

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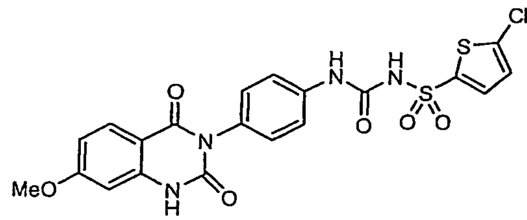

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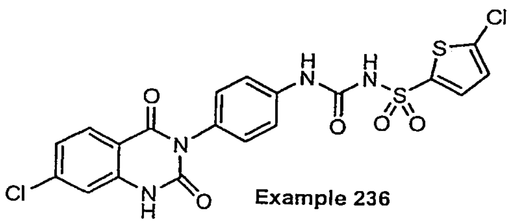

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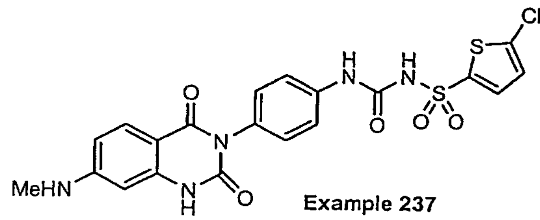

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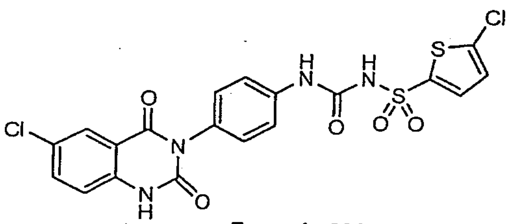

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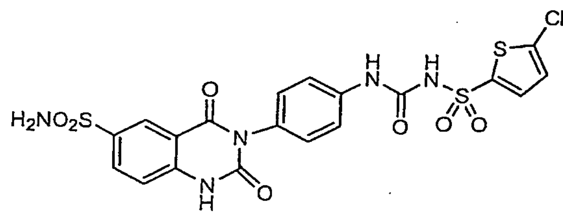

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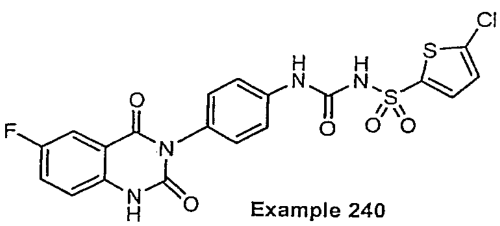

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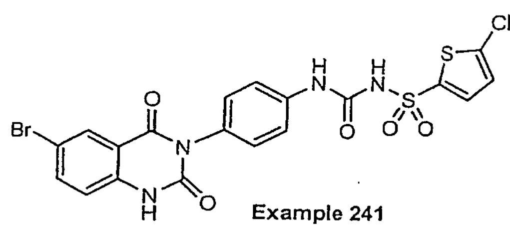

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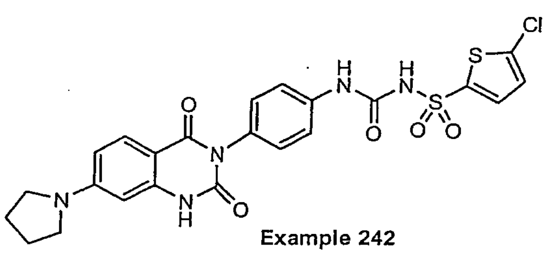

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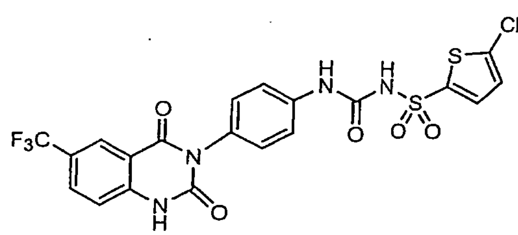

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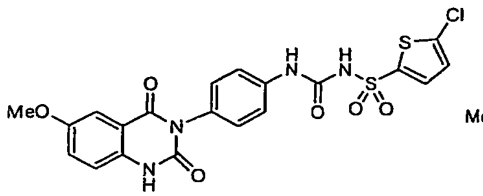

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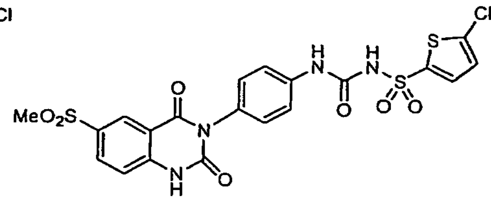

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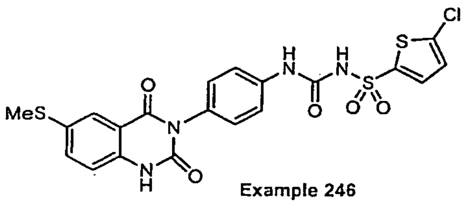

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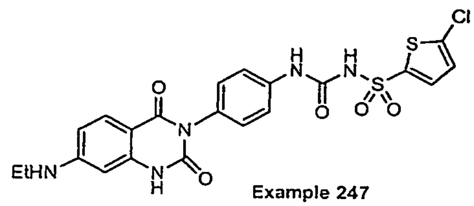

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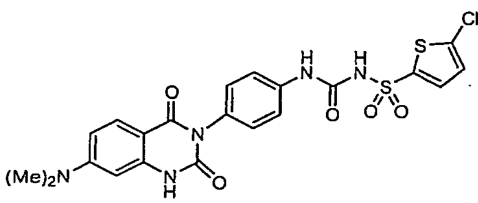

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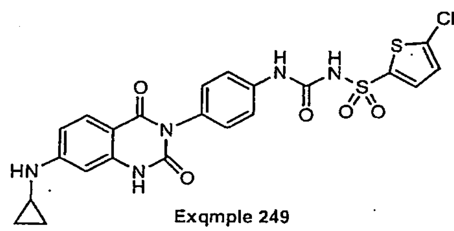
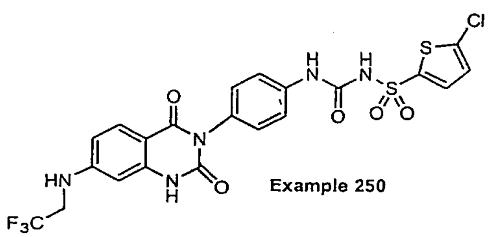


Exqmple 249



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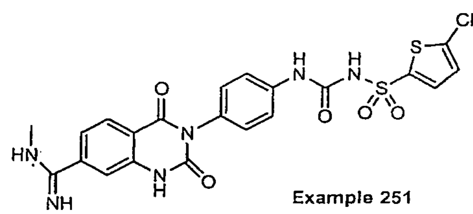

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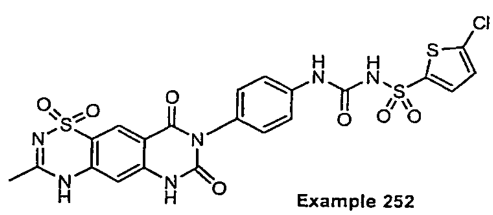

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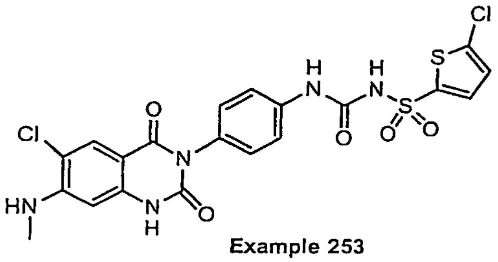

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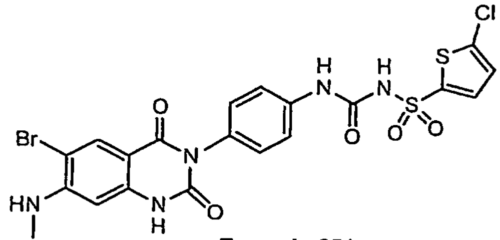

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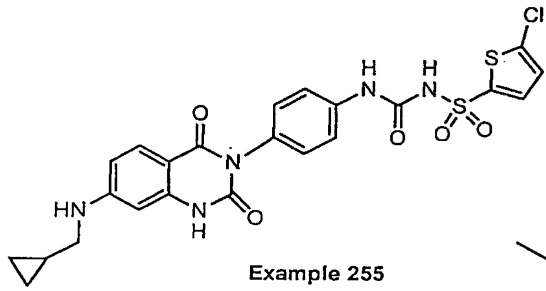

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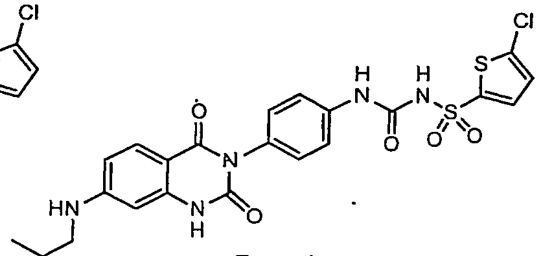

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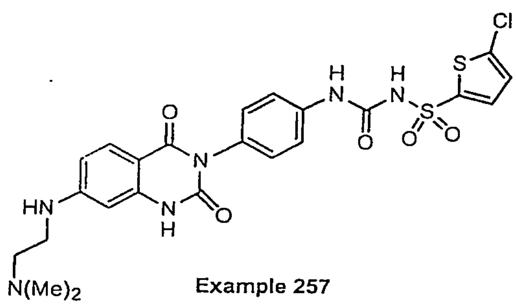

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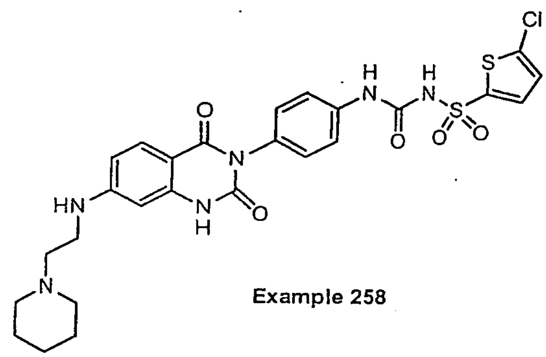

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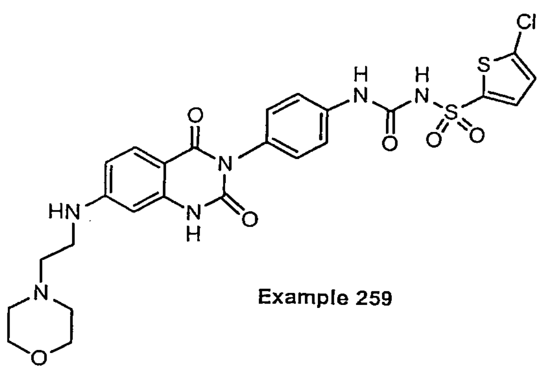

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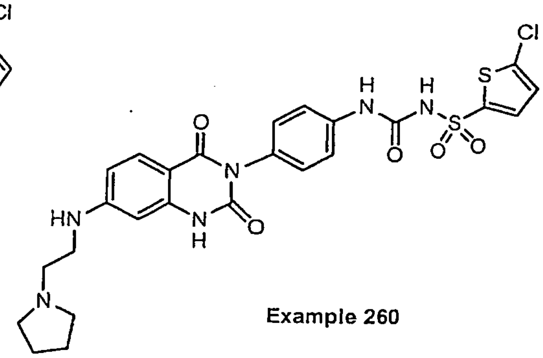

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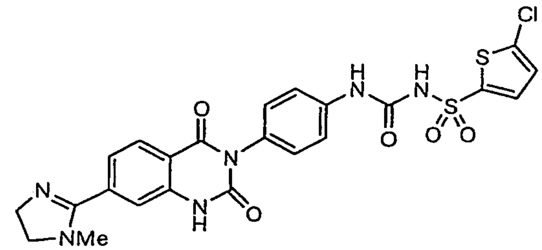

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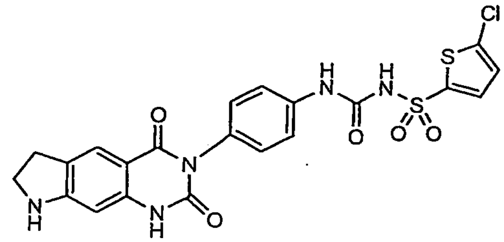

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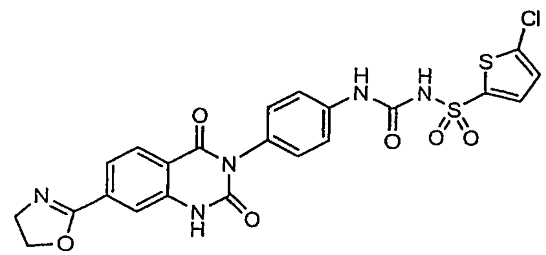

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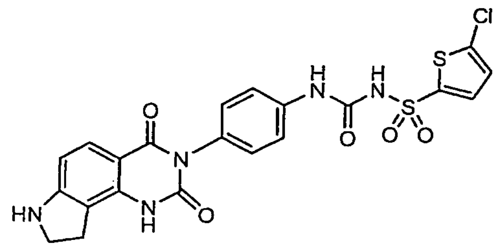

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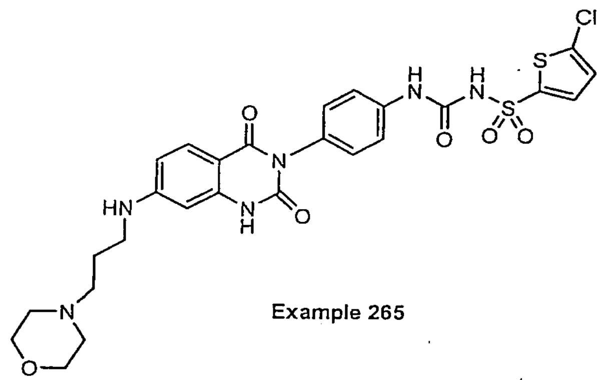

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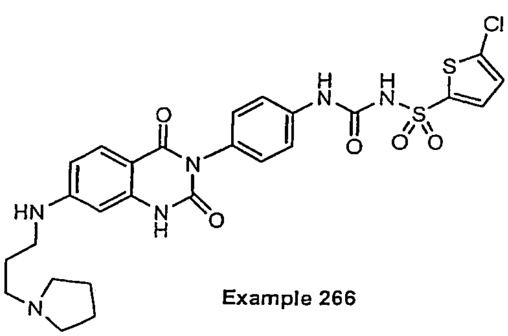

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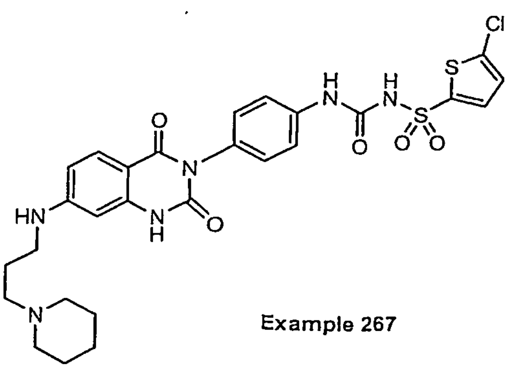

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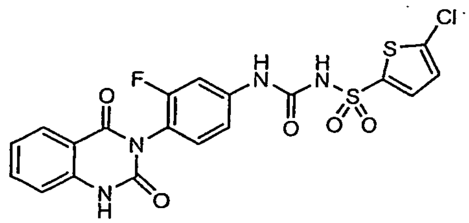

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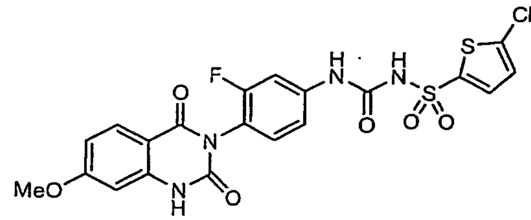

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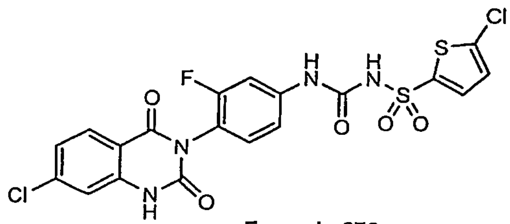

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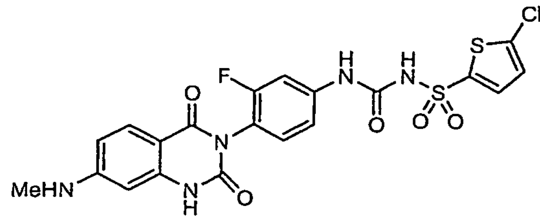

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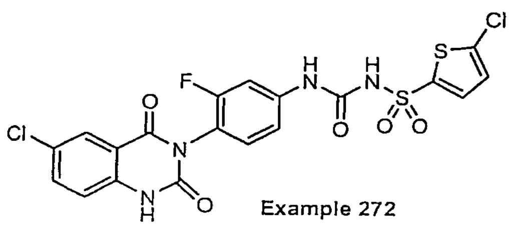

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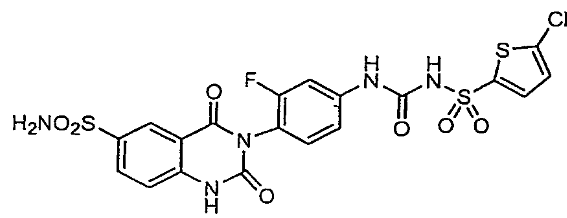

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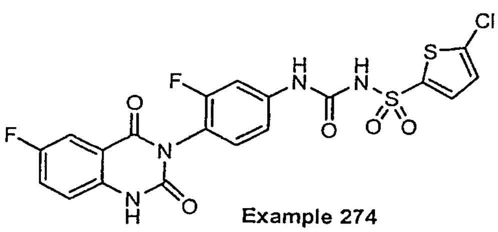

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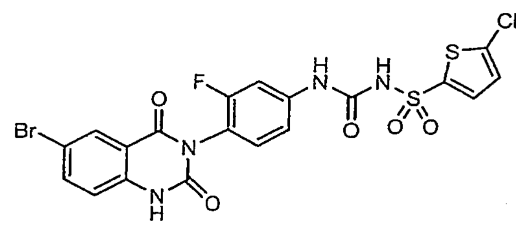

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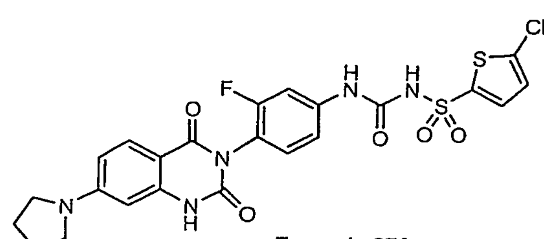

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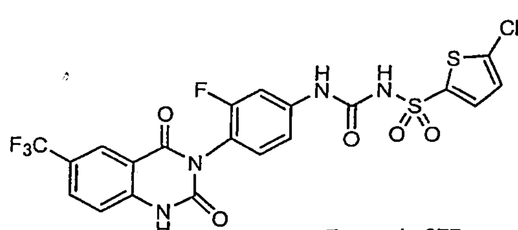

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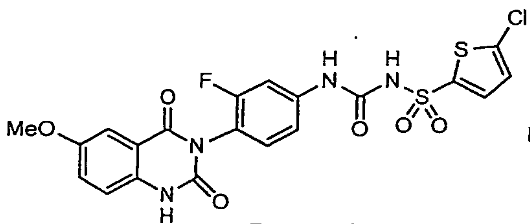

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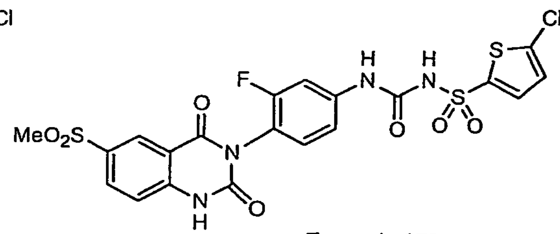

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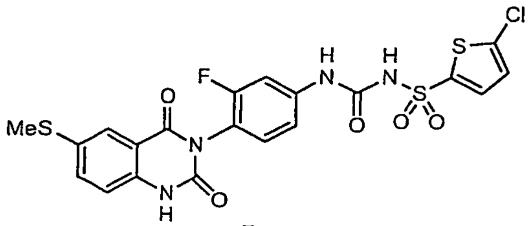

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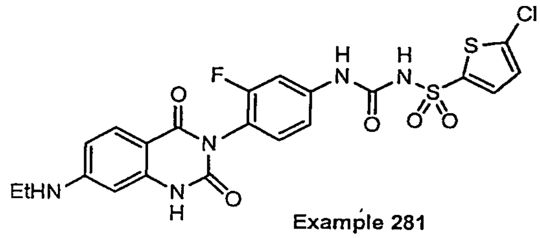

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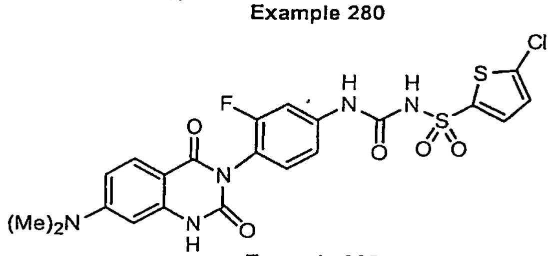

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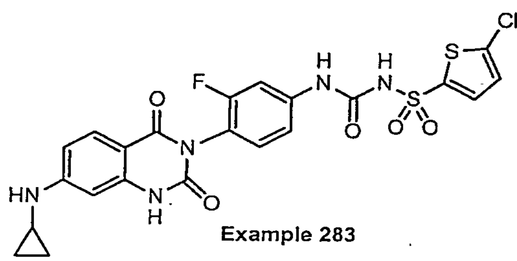

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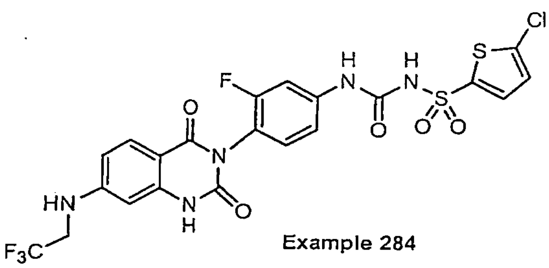

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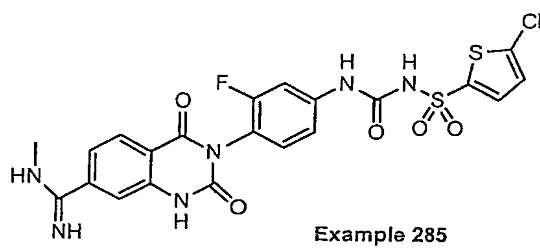

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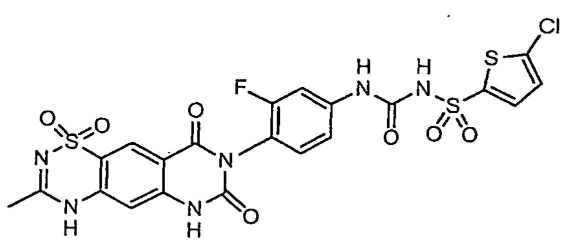

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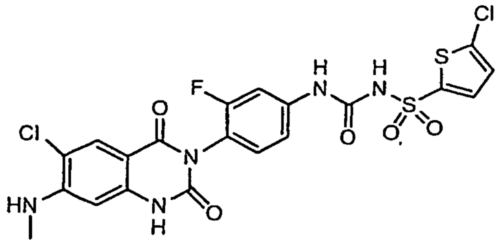

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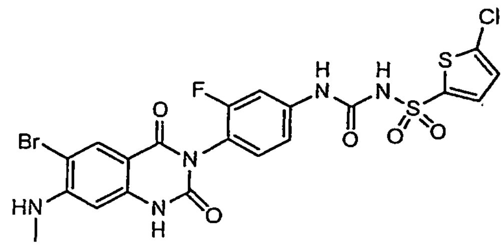

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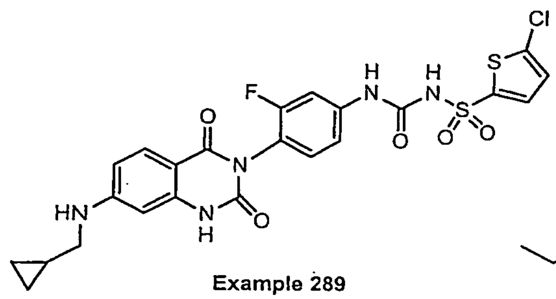

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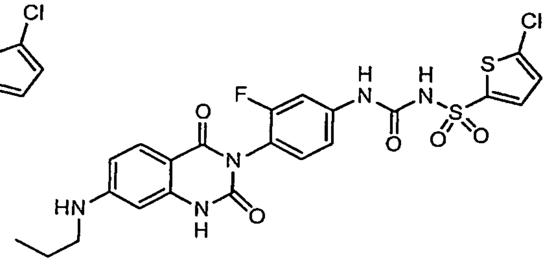

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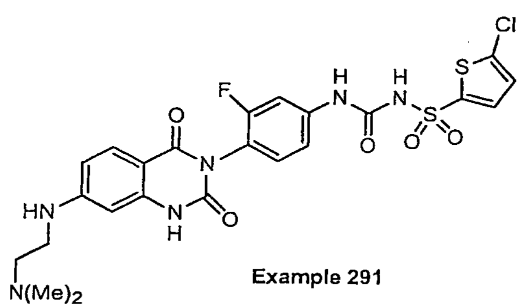
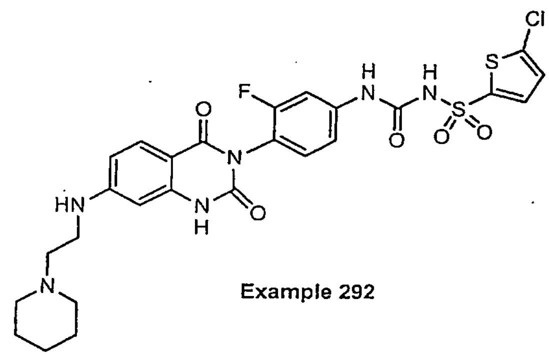
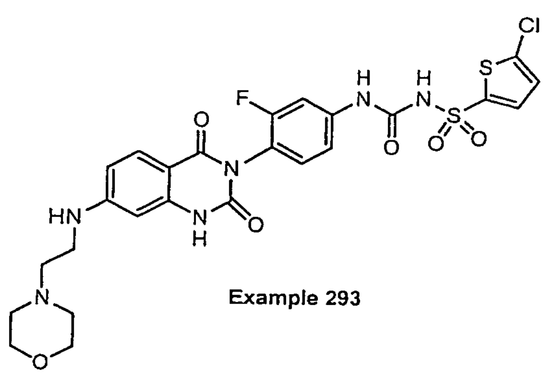


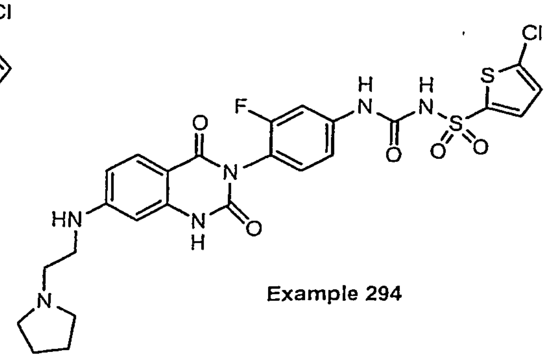
Example 291



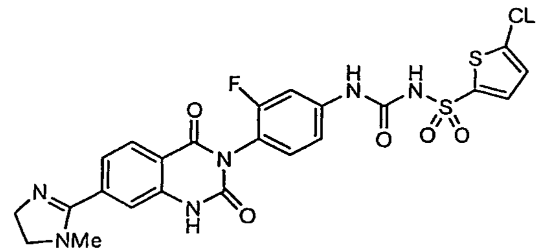
Example 292



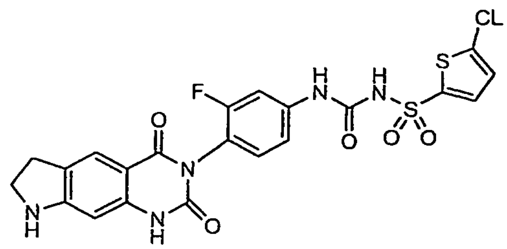
Example 293



Example 294



Example 295



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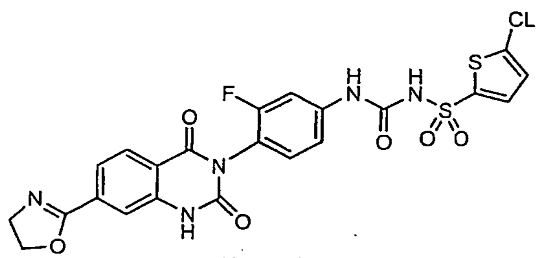

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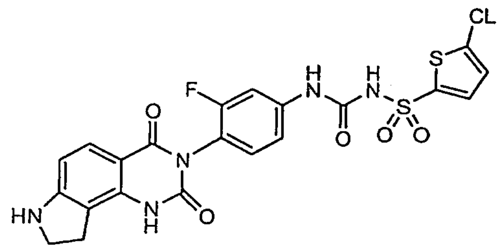

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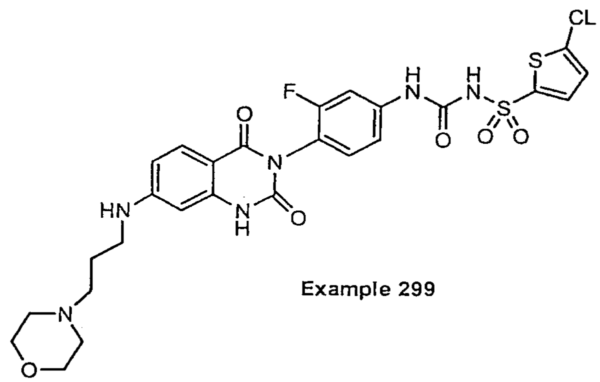

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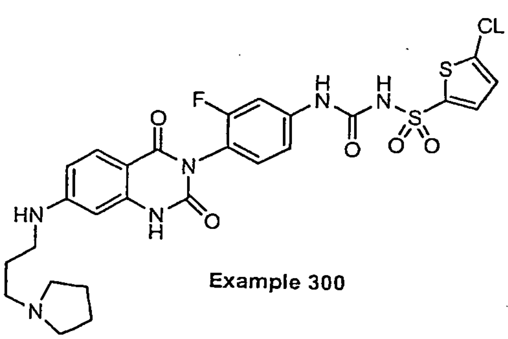

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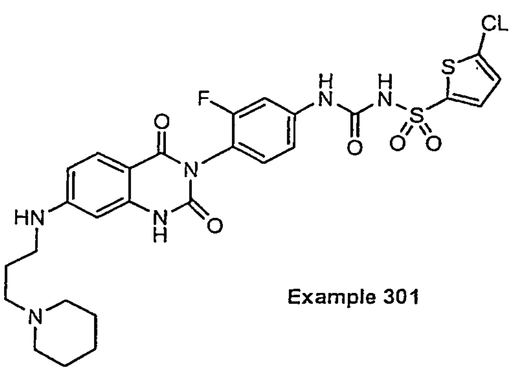

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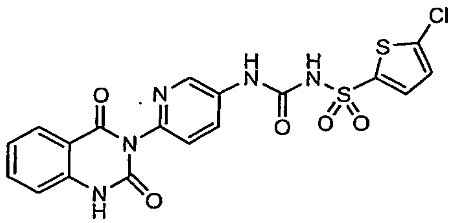

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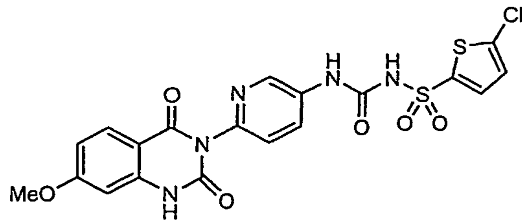
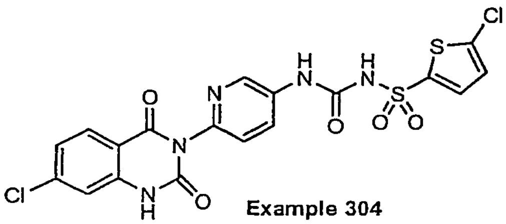
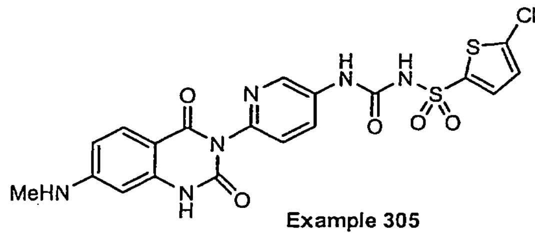


Example 303



Example 304



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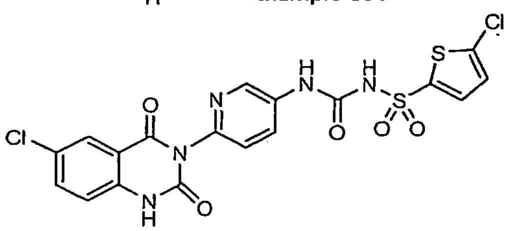
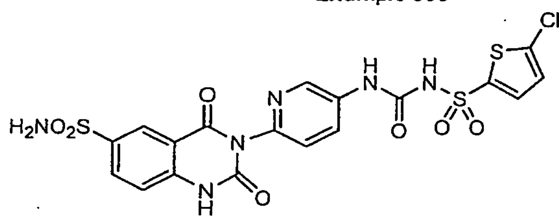
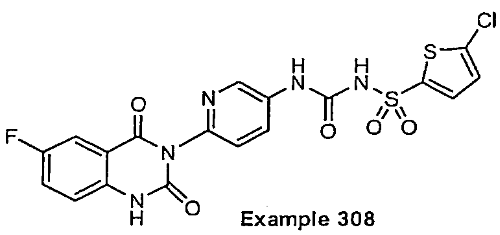


Exmaple 306



example 307



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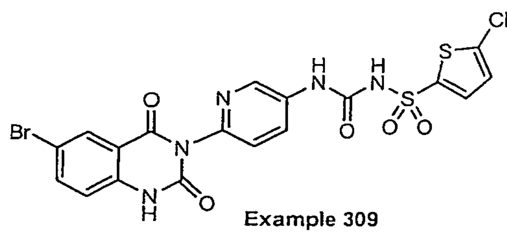
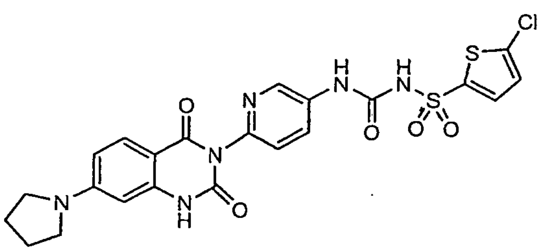


Example 309



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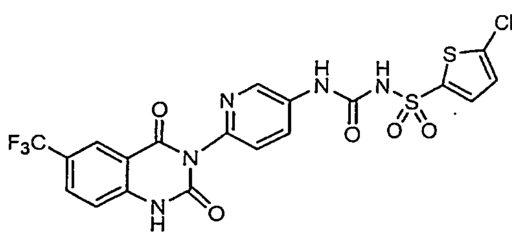

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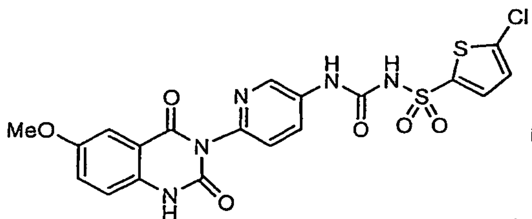
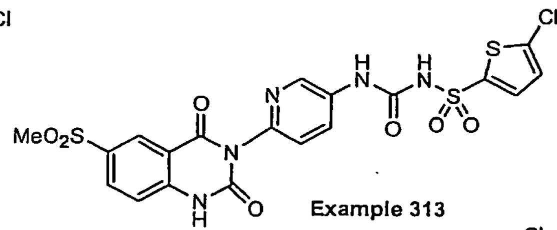


Example 312



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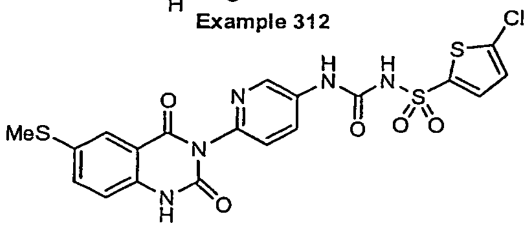

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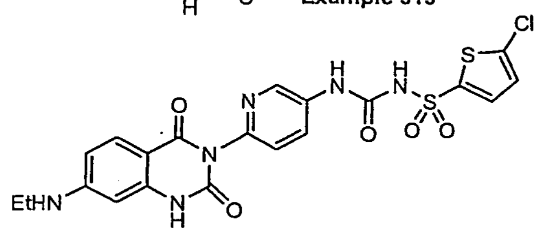
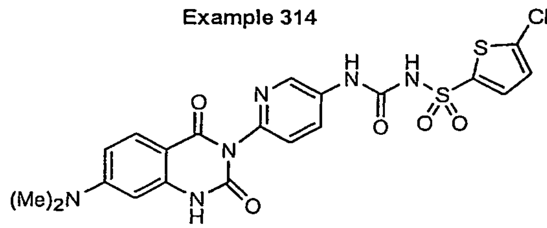


Example 315



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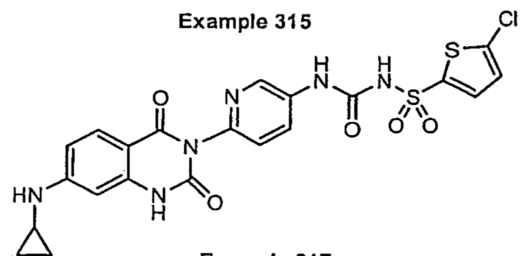

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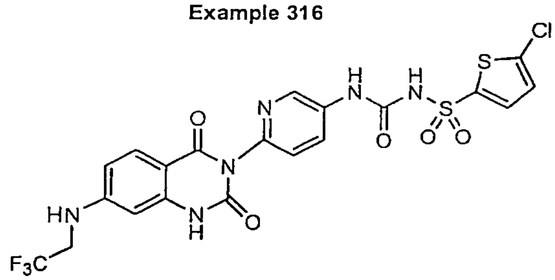

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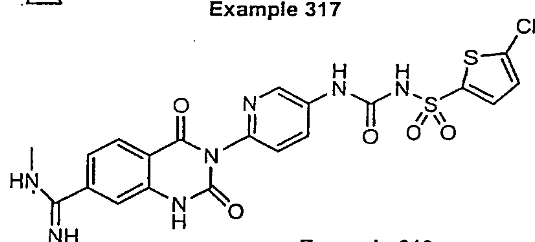

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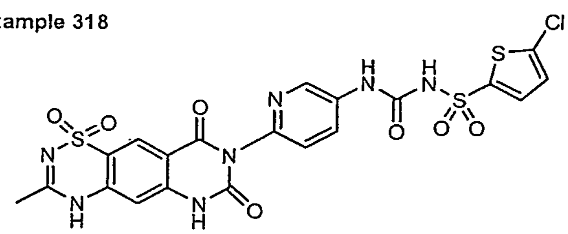

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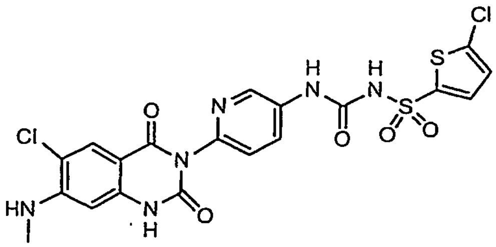

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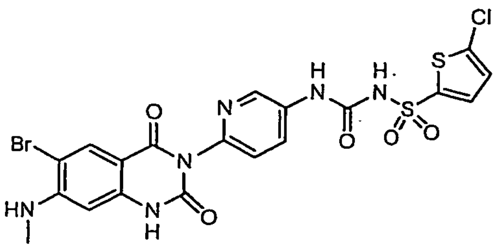

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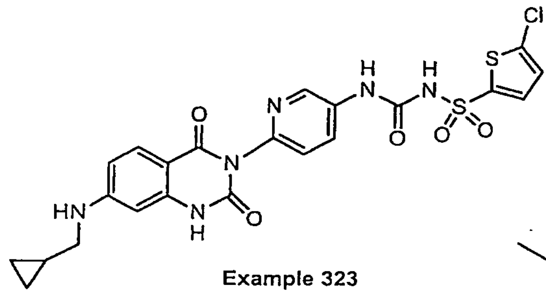

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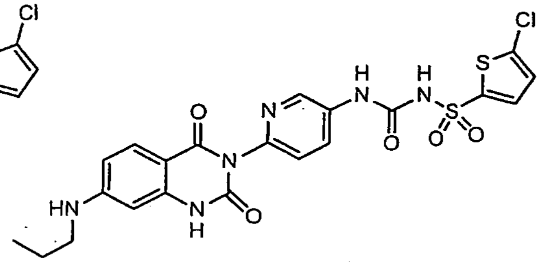

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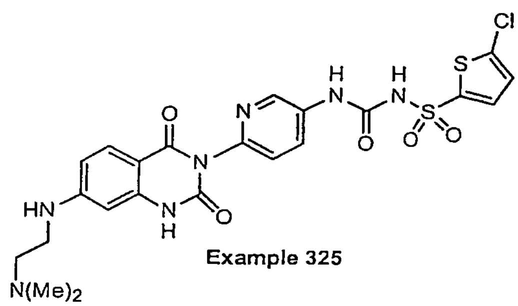

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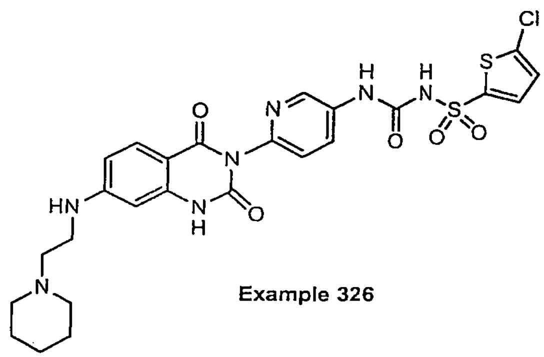

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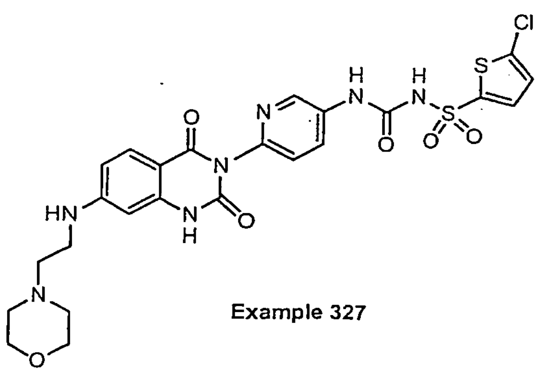

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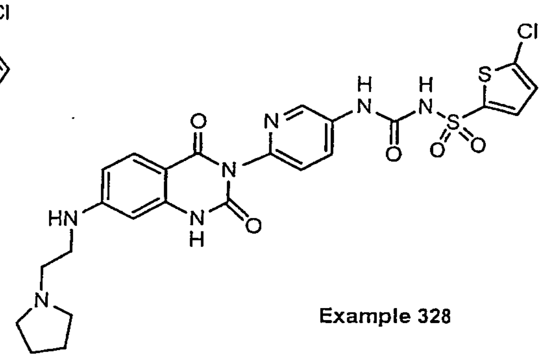

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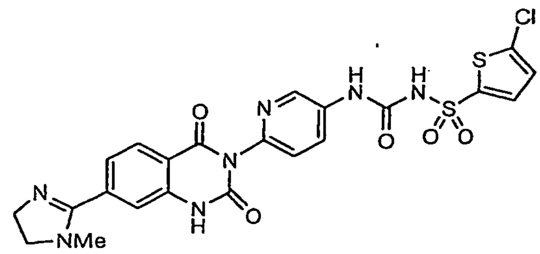

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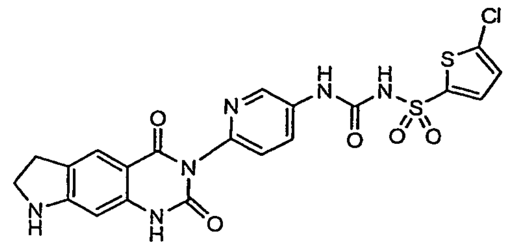

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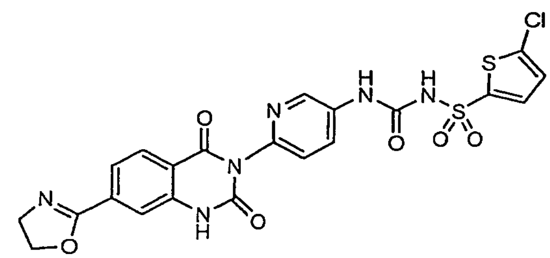

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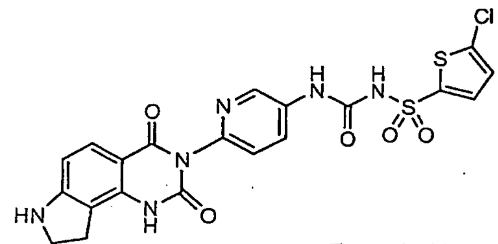

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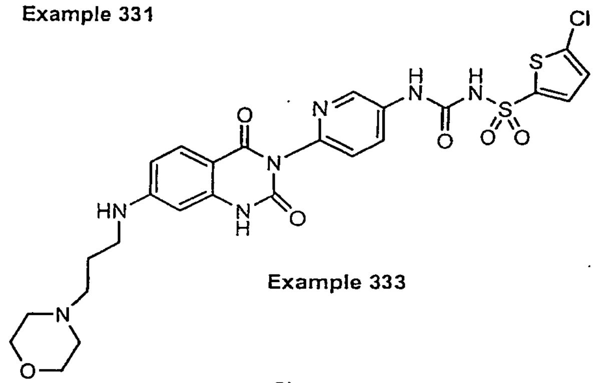

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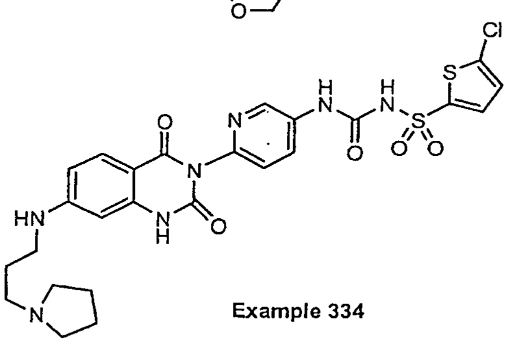

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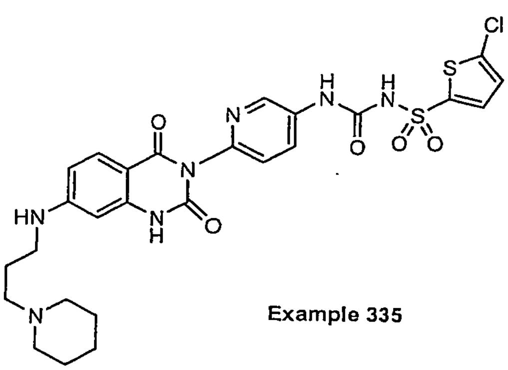

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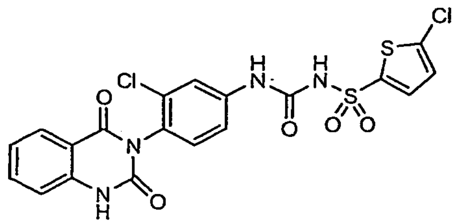

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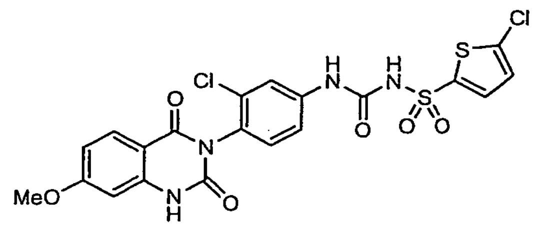

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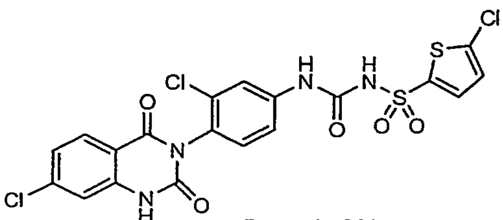

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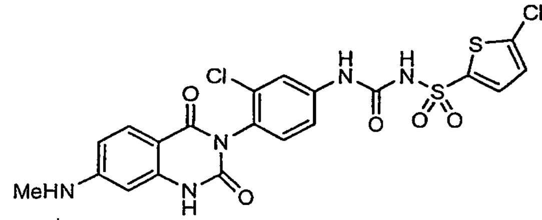

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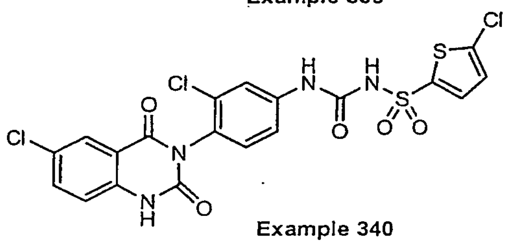

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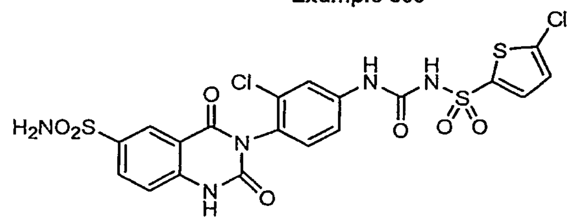

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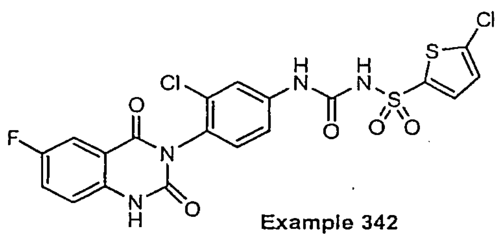

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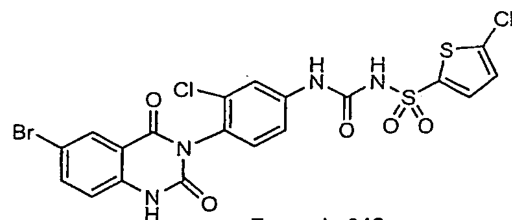

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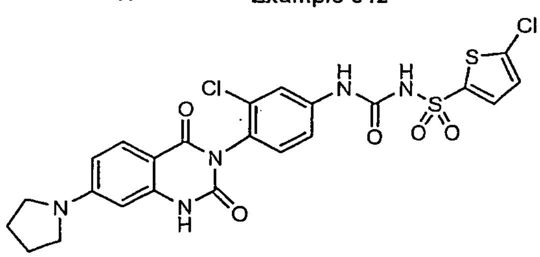

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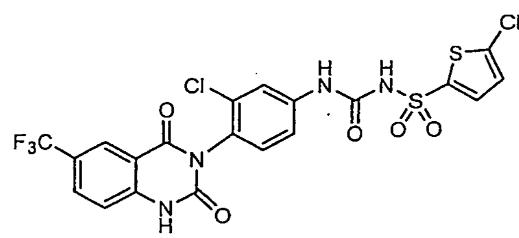

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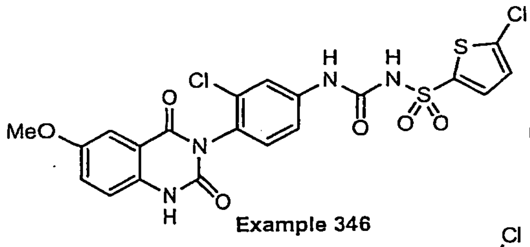

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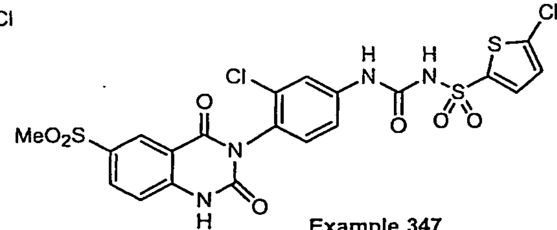

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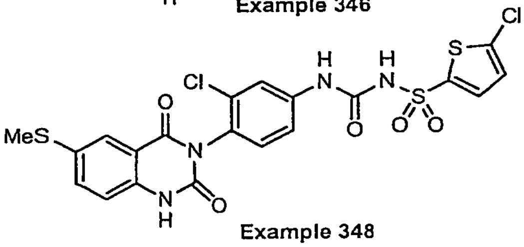

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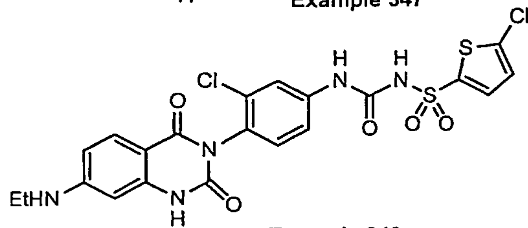

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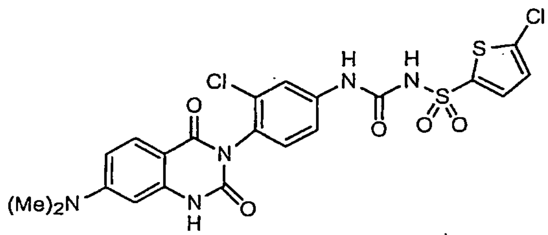

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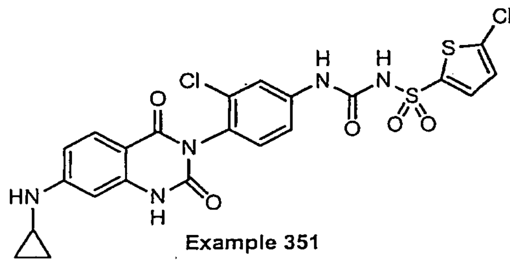

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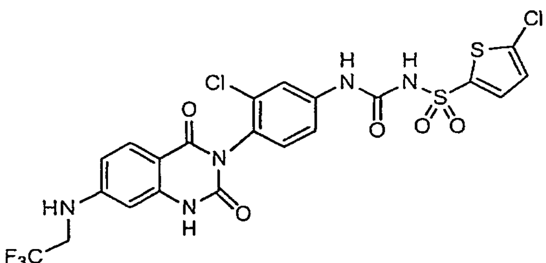

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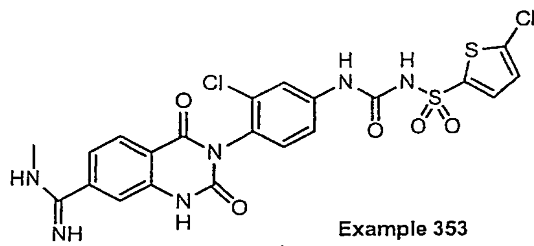

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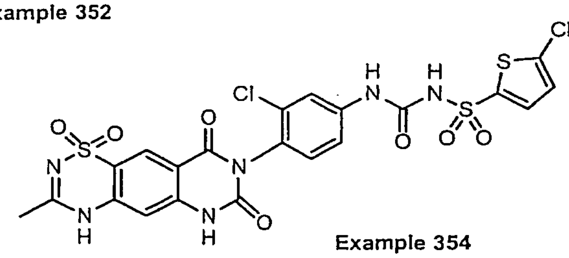

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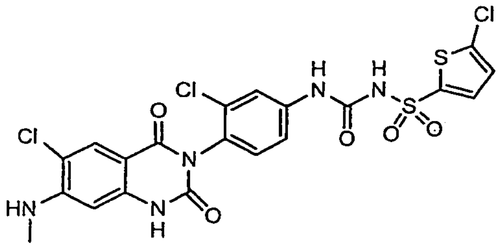

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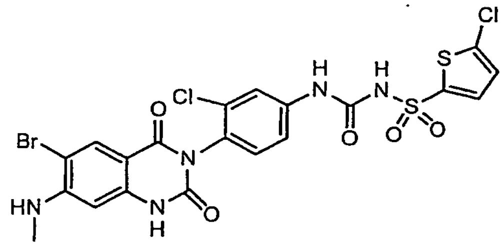

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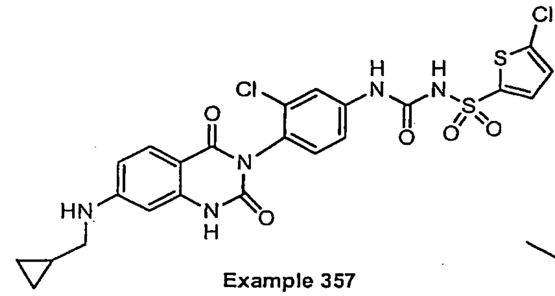

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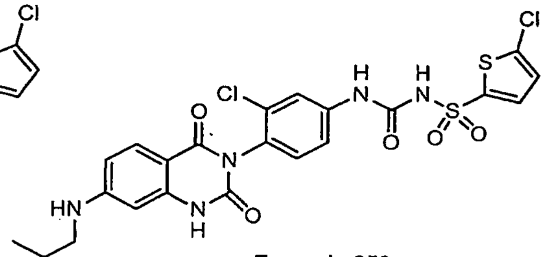

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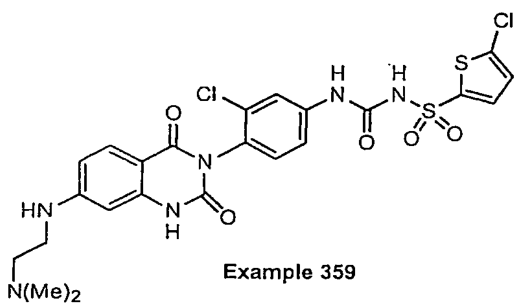

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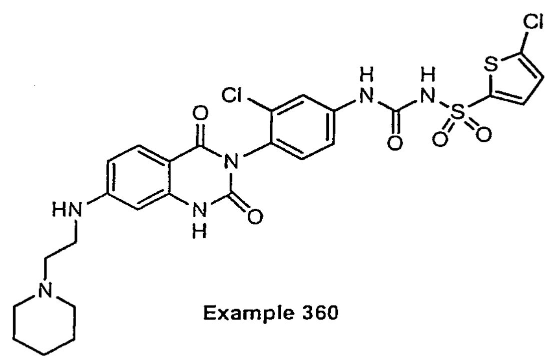

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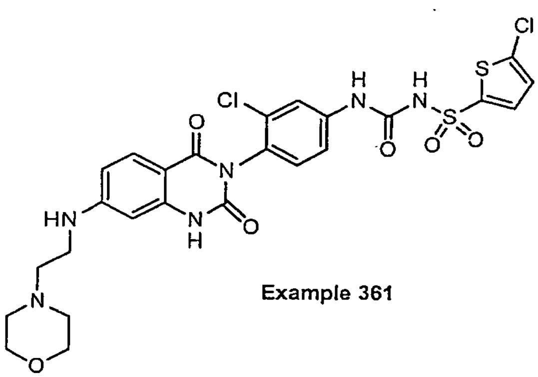

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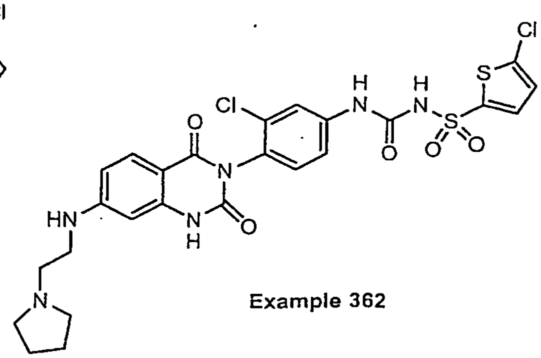

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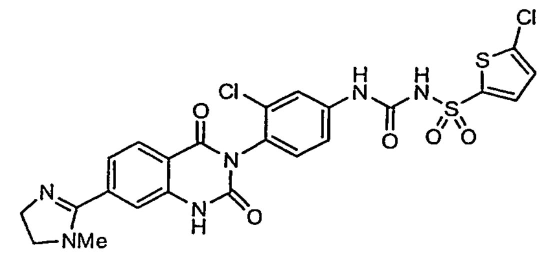

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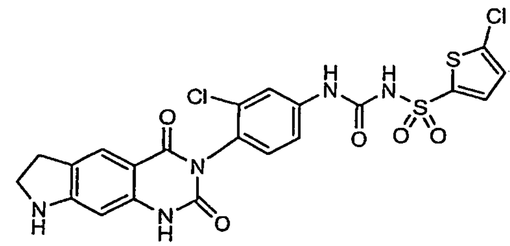

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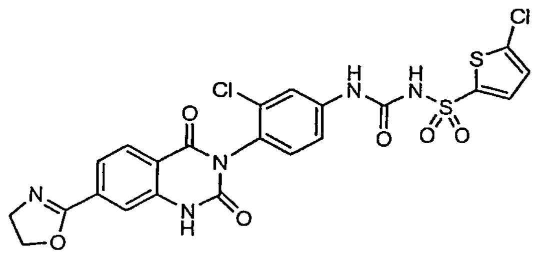

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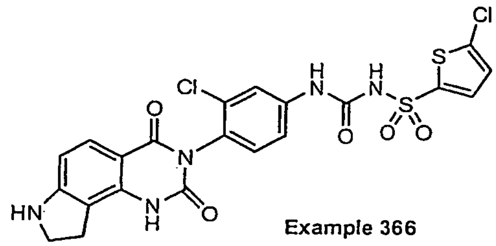
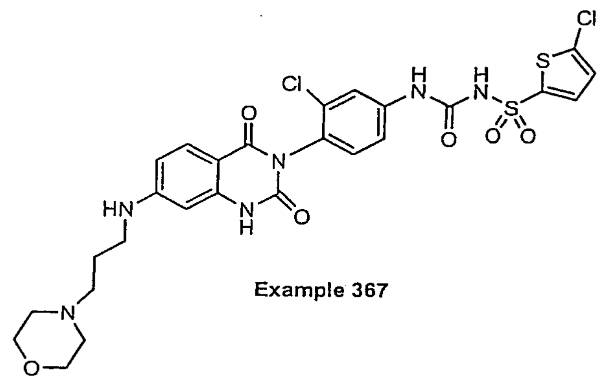
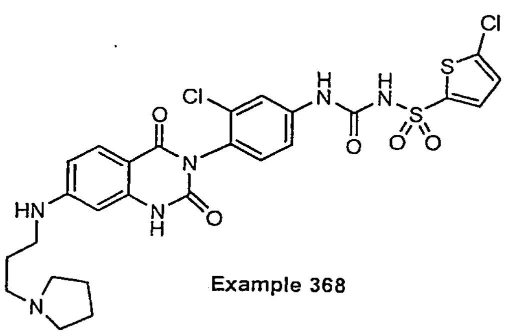


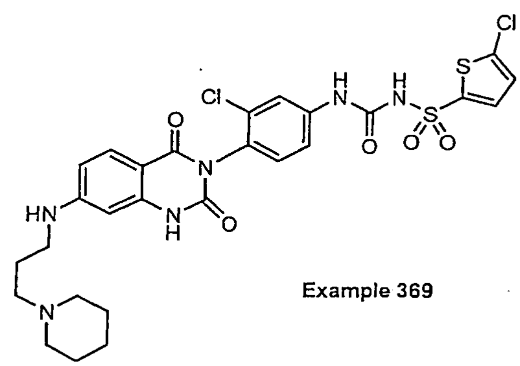
Example 366



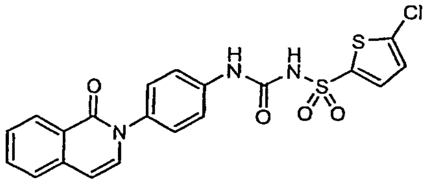
Example 367



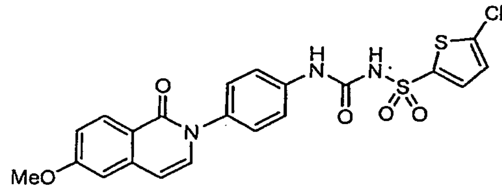
Example 368



Example 369



Example 370



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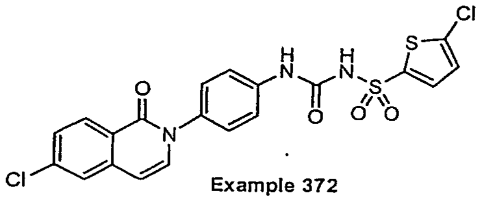
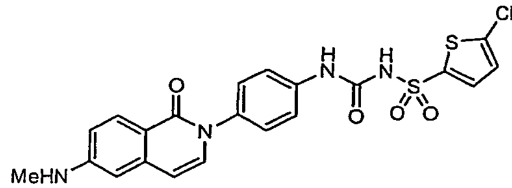


Example 372



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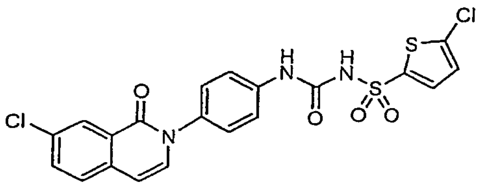

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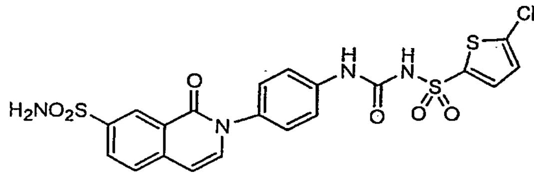

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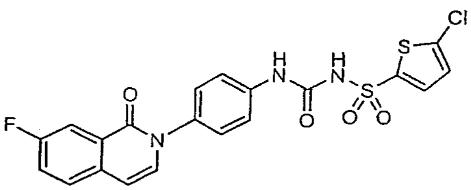

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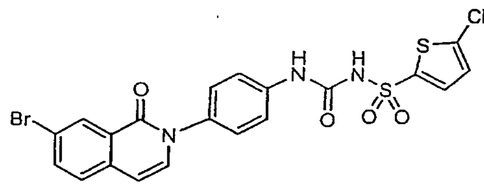

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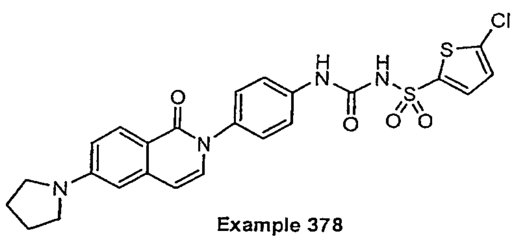

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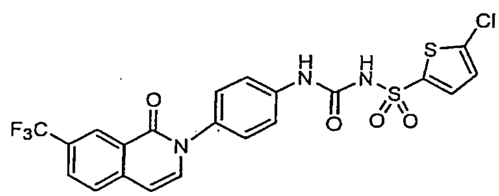

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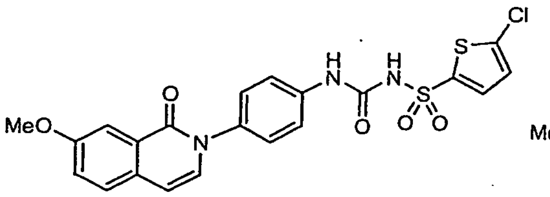

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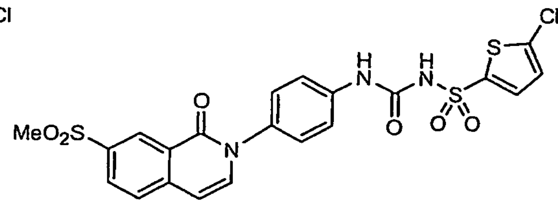

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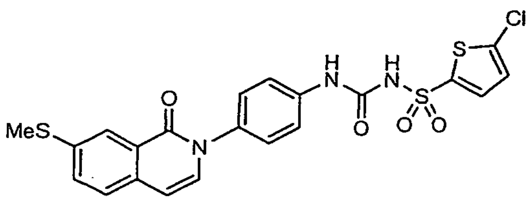

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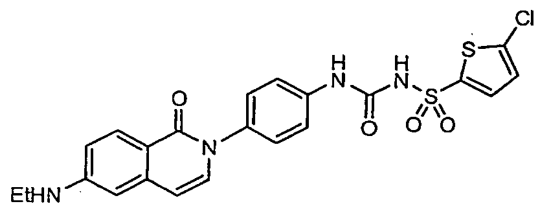

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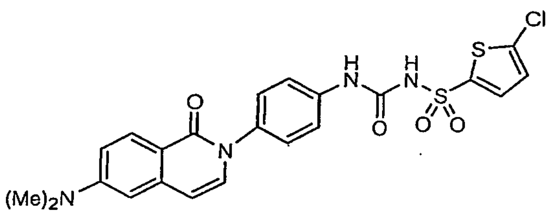

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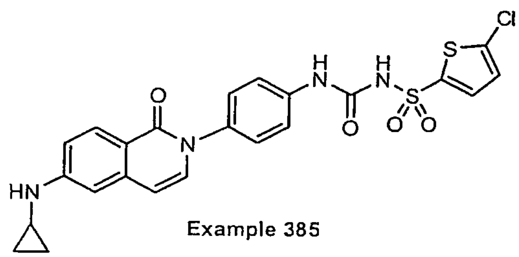

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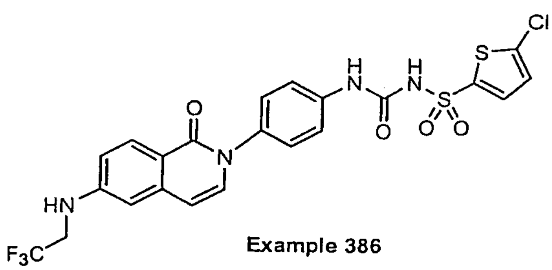

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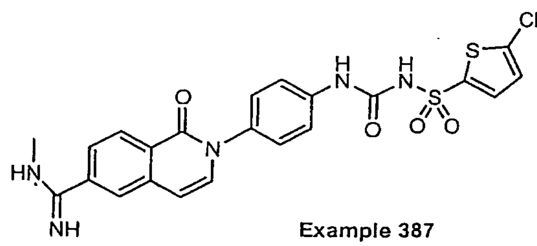

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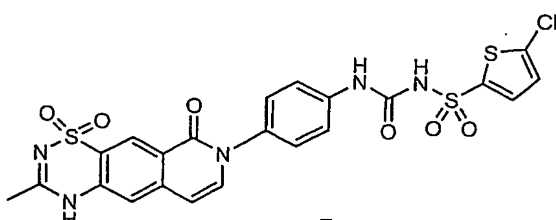
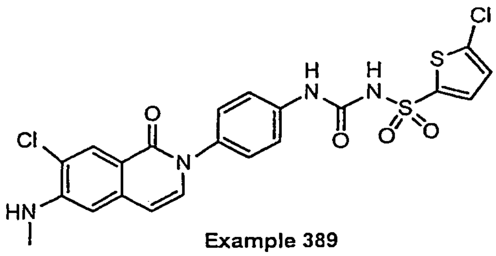


Example 388



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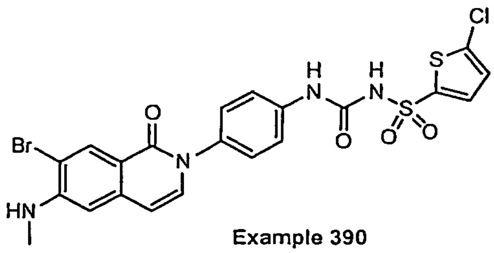
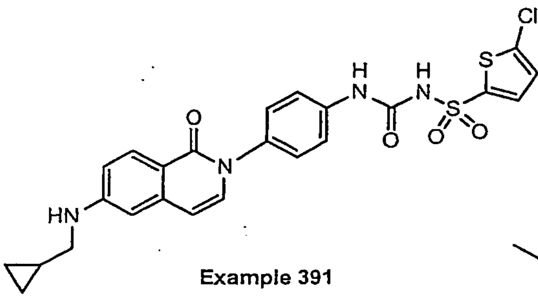
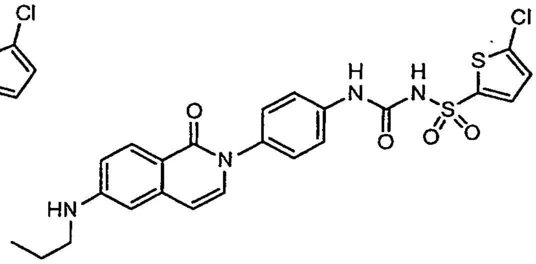


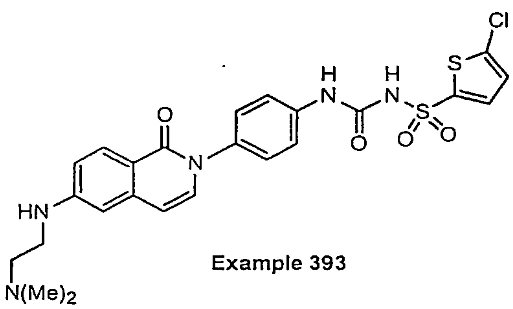
Example 390



Example 391



Example 392



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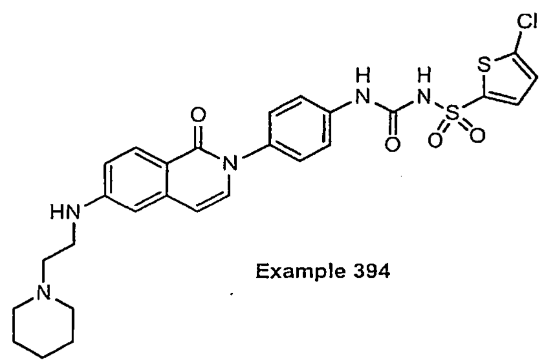

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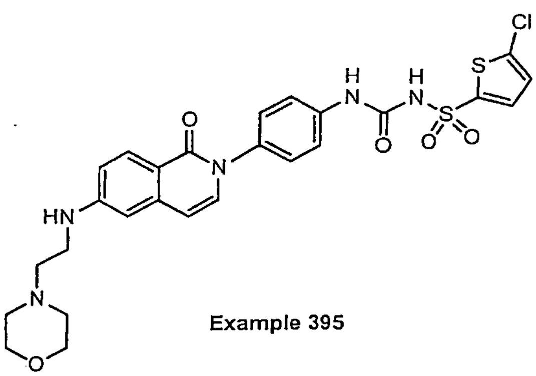

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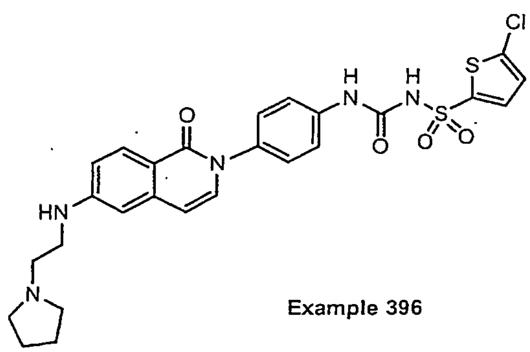

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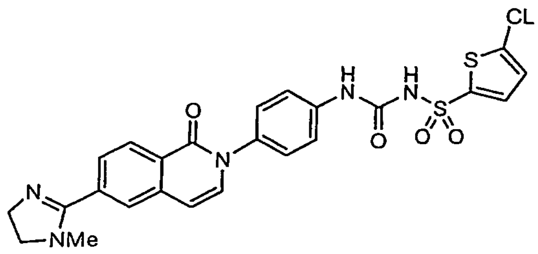

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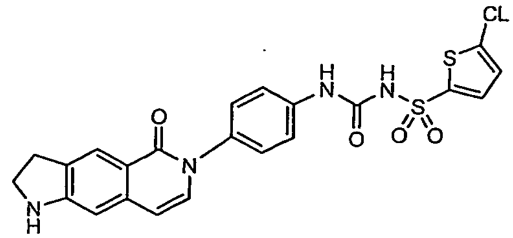

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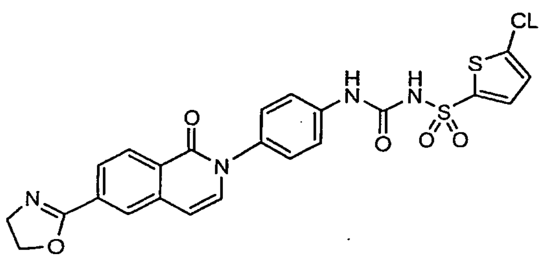

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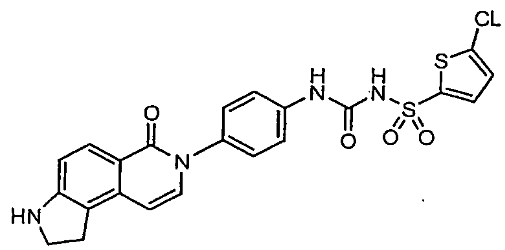
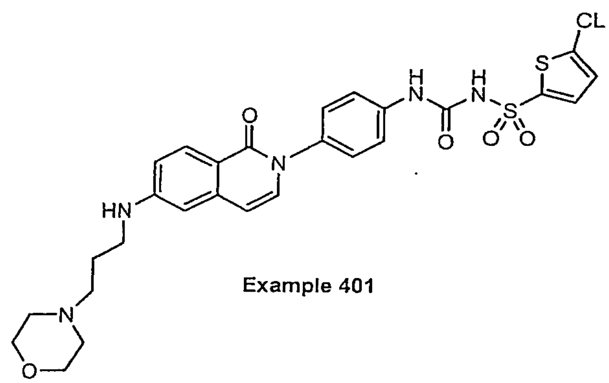
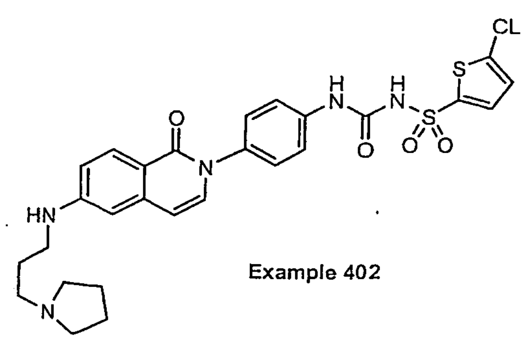


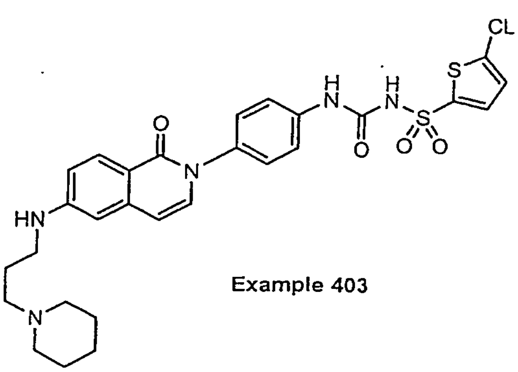
Example 400



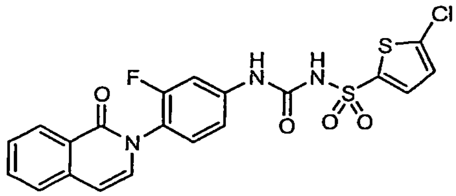
Example 401



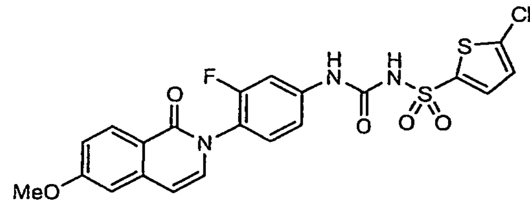
Example 402



Example 403



Example 404



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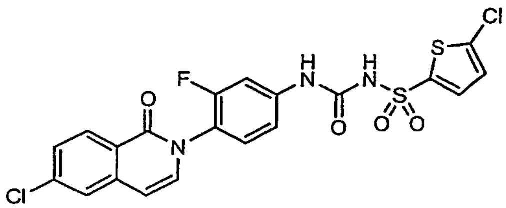
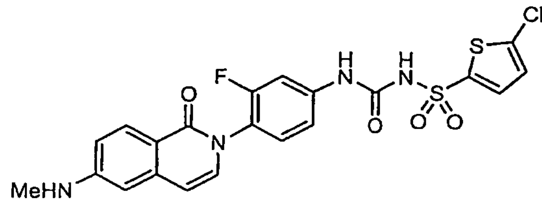
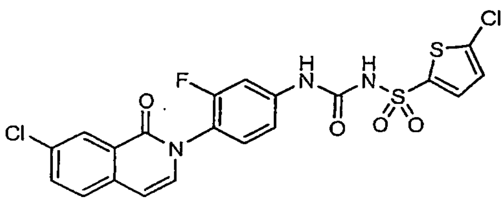


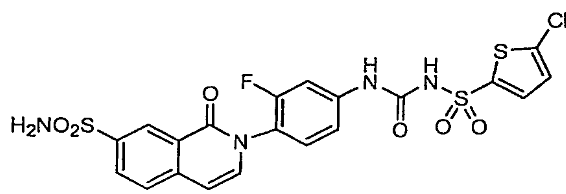
Example 406



Example 407



Example 408



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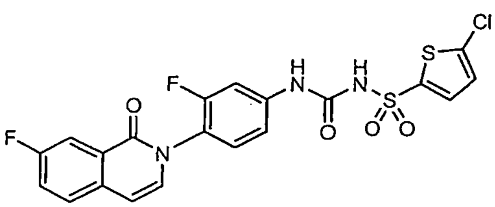

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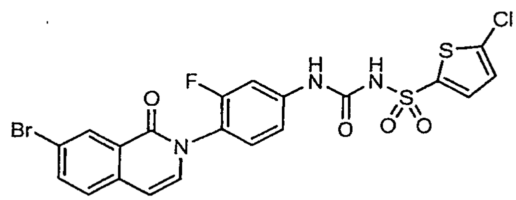
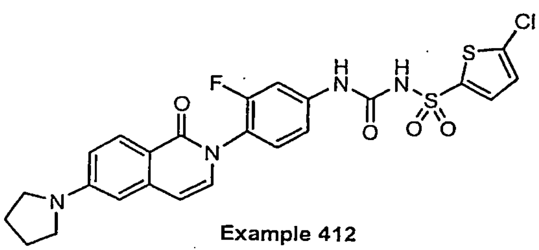
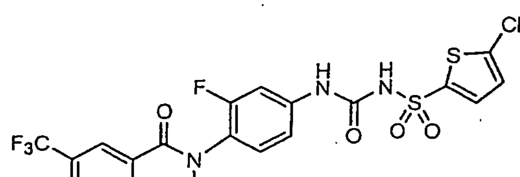


Example 411



Example 412



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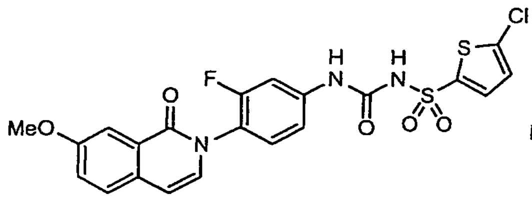

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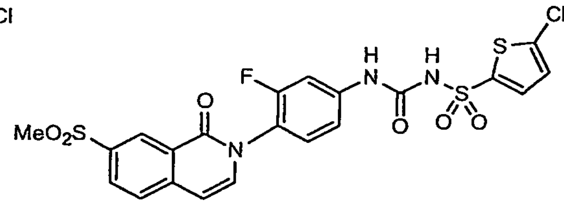
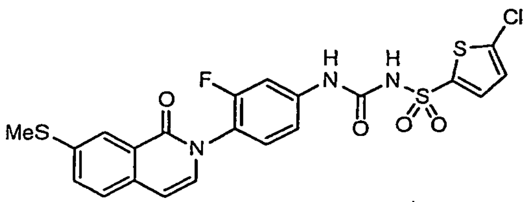


Example 415



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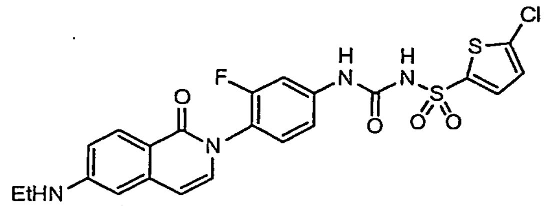

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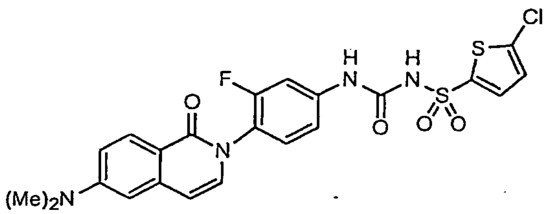
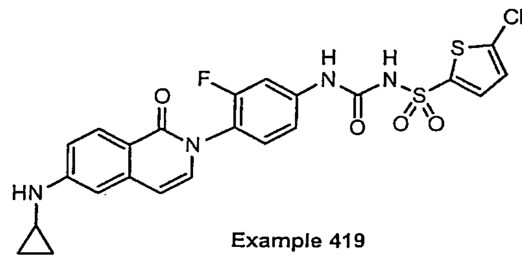
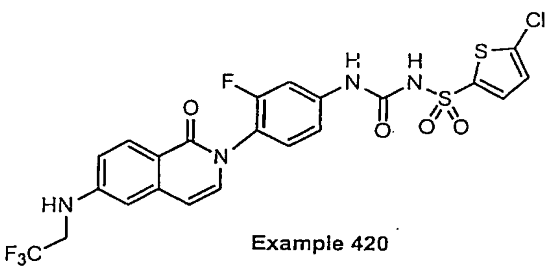


Example 418



Example 419



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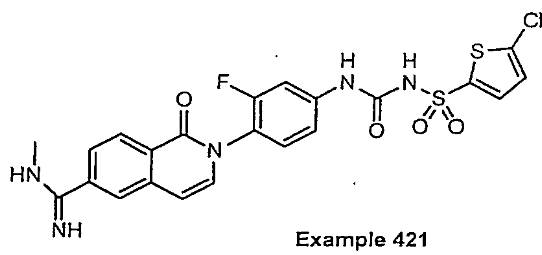
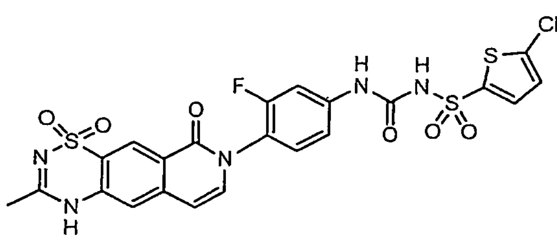


Example 421



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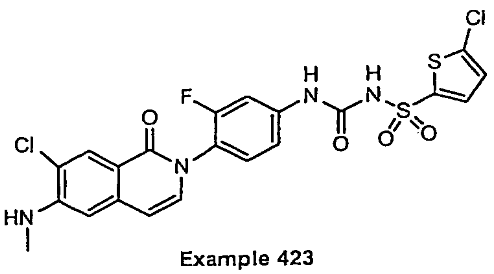

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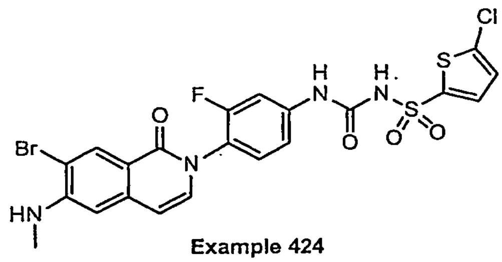

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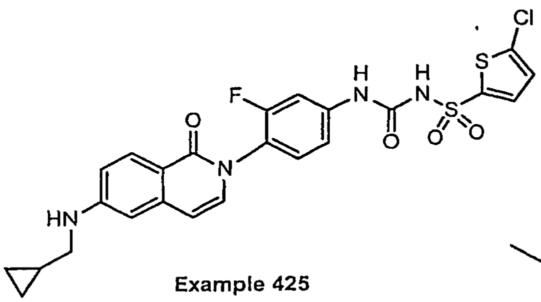
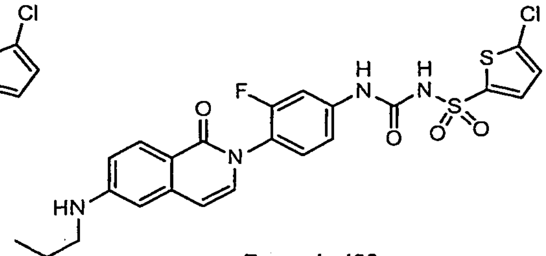
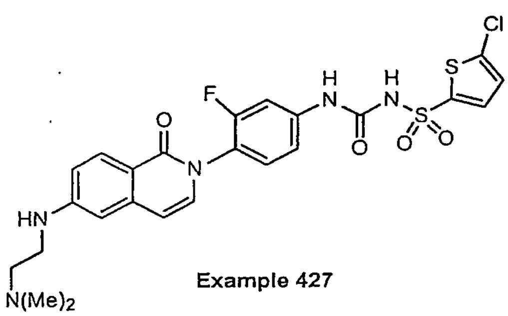


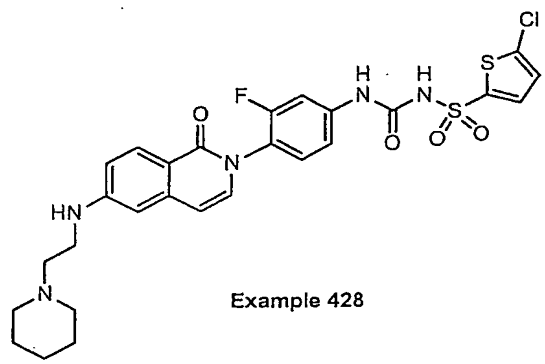
Example 425



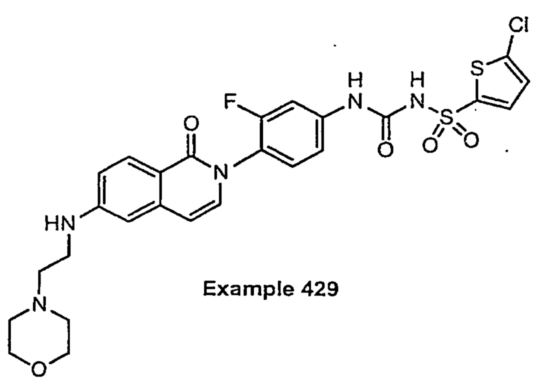
Example 426



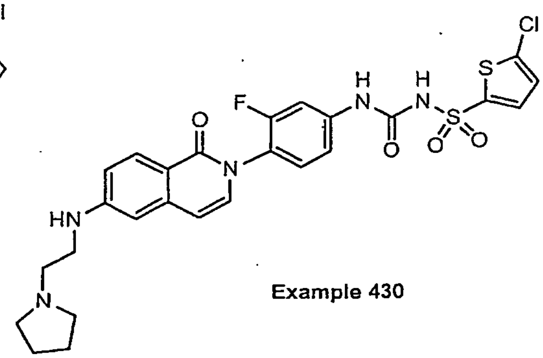
Example 427



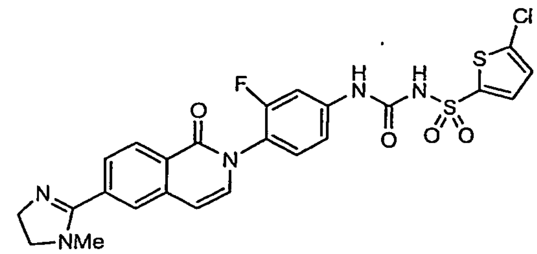
Example 428



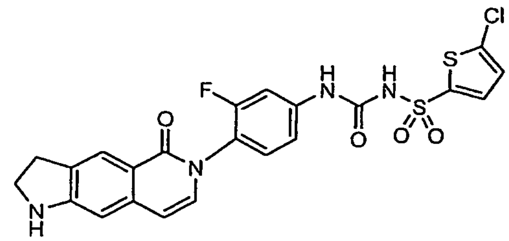
Example 429



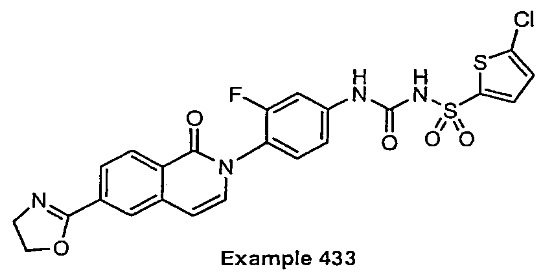
Example 430



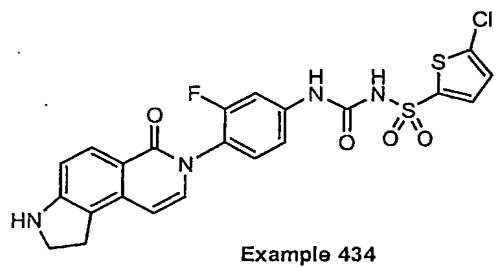
Example 431



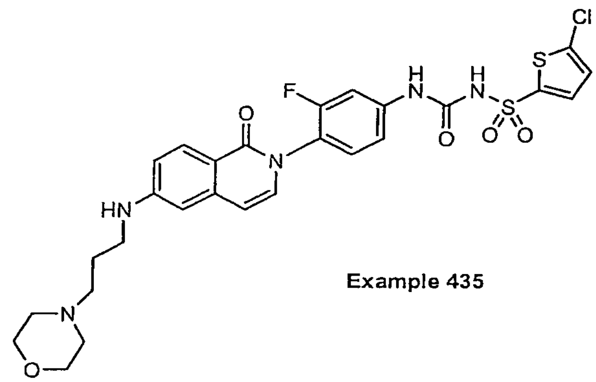
Example 432



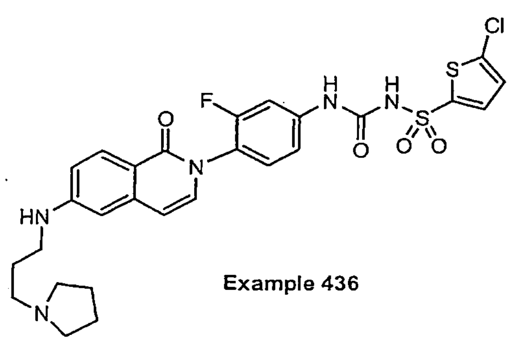
Example 433



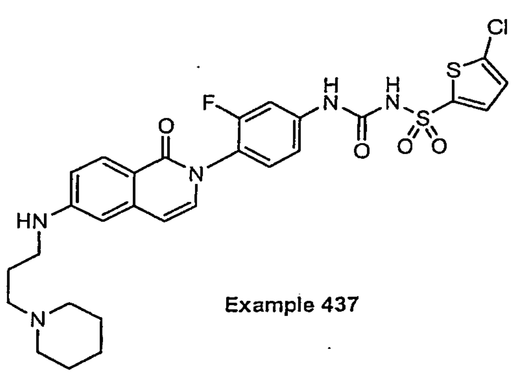
Example 434



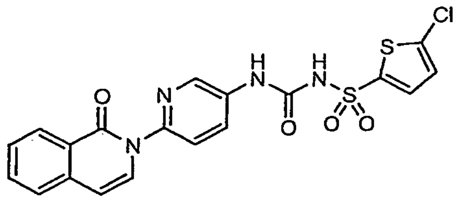
Example 435



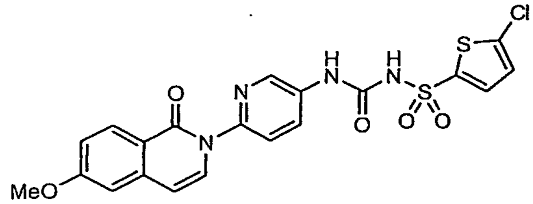
Example 436



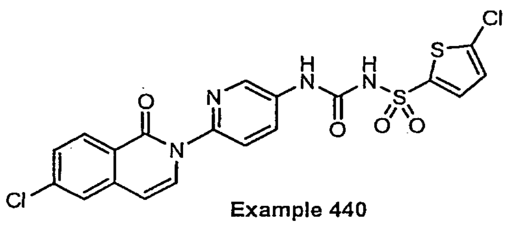
Example 437



Example 438



Example 439



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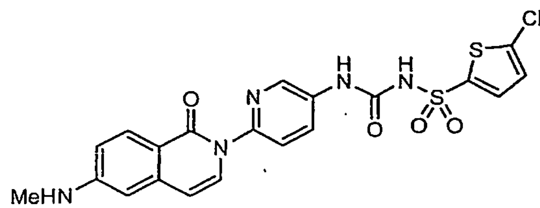
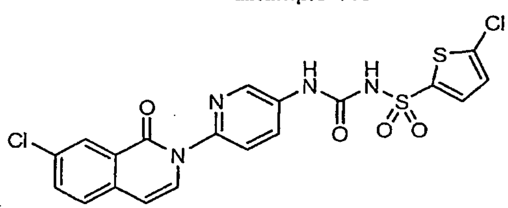
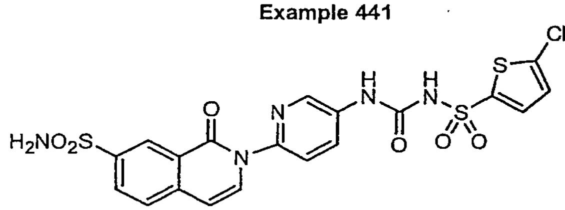


Example 441



Example 442



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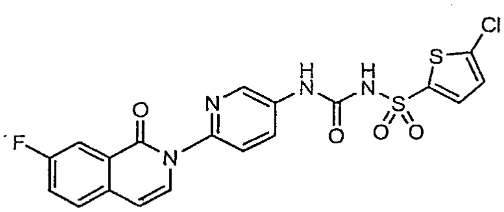

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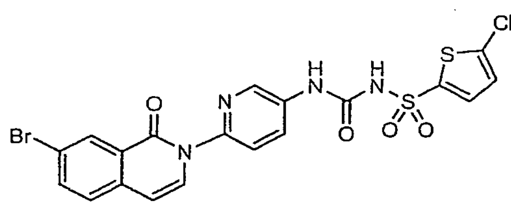

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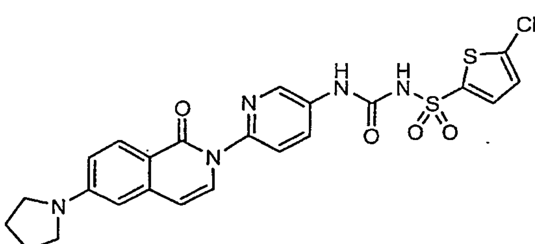

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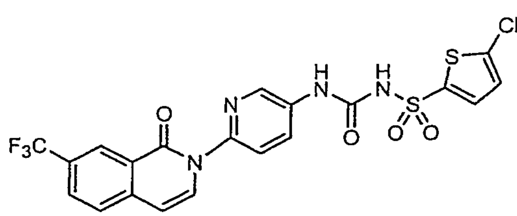
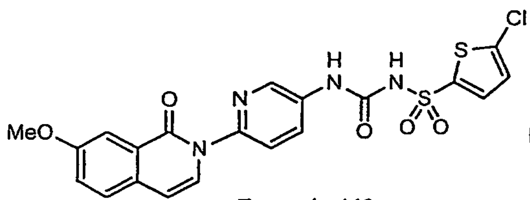
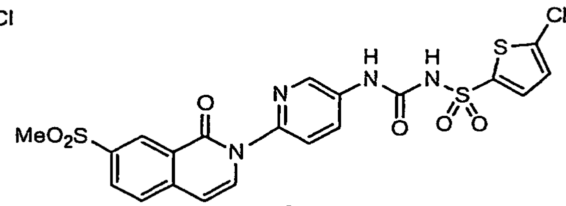


Example 447



Example 448



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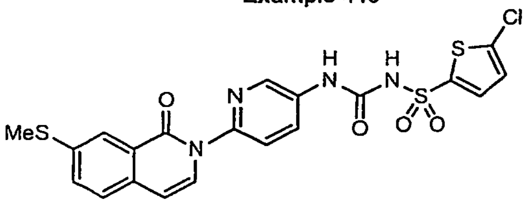

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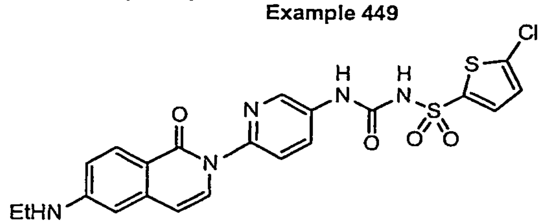

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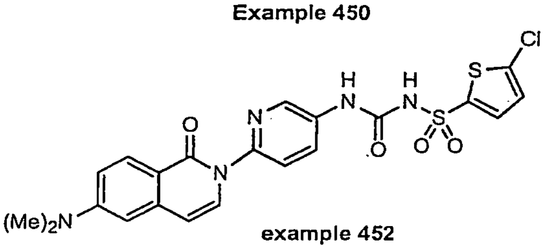
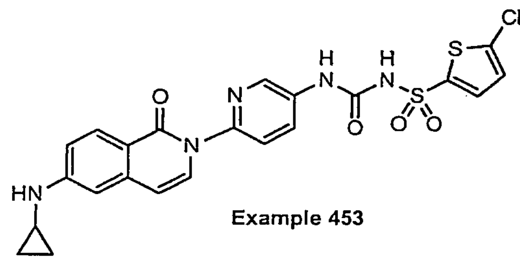


example 452



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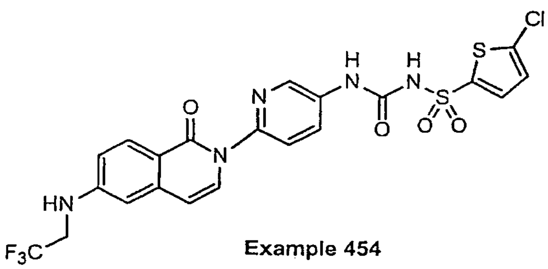

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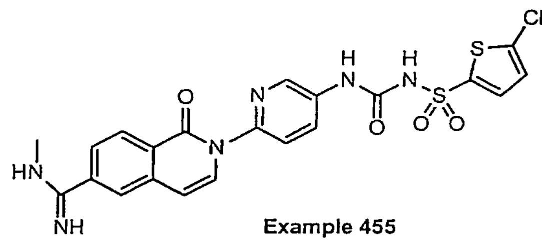

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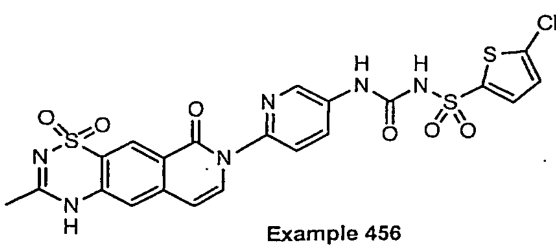

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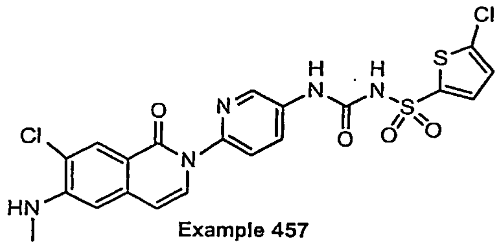
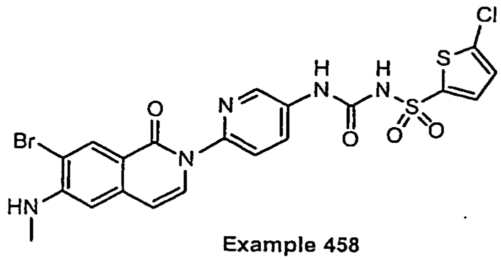
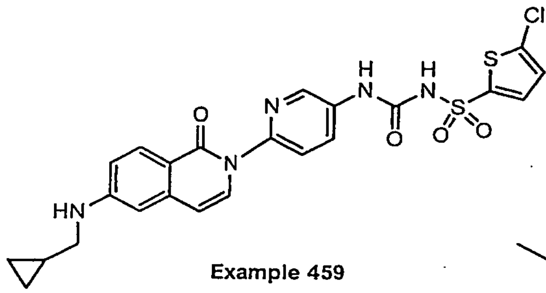


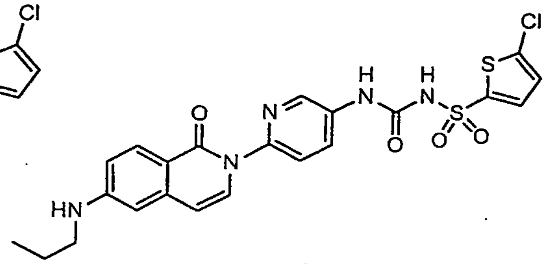
Example 457



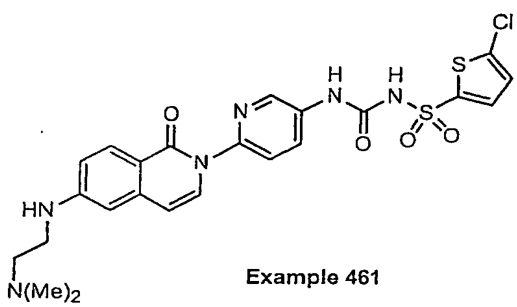
Example 458



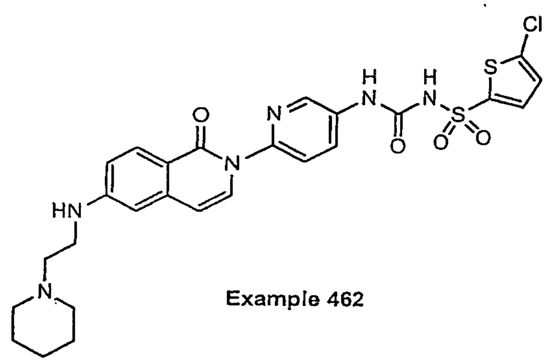
Example 459



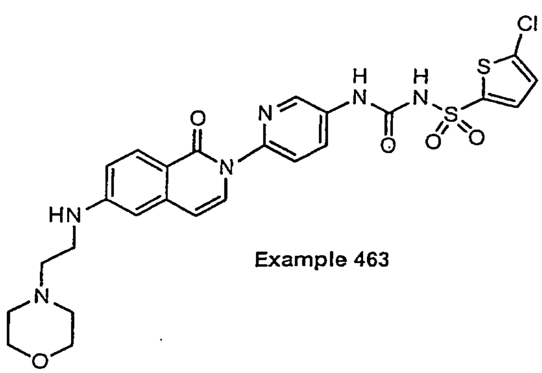
example 460



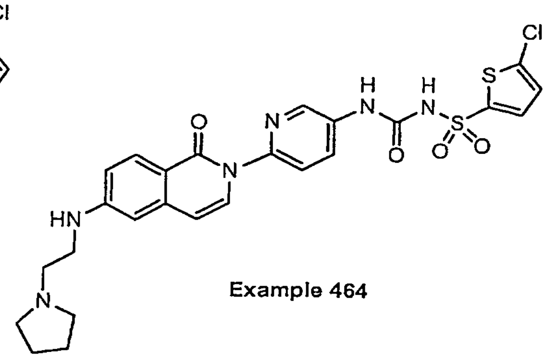
Example 461



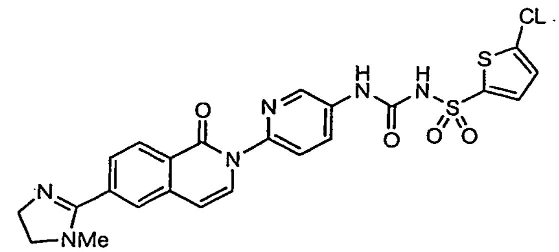
Example 462



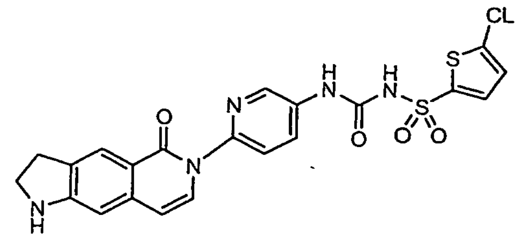
Example 463



Example 464



Example 465



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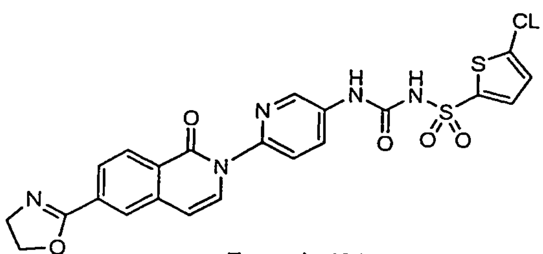

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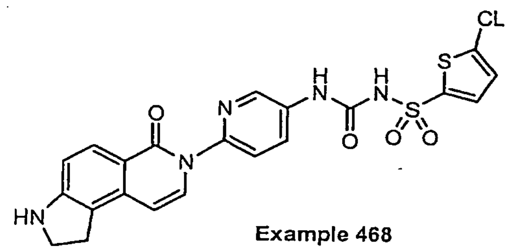

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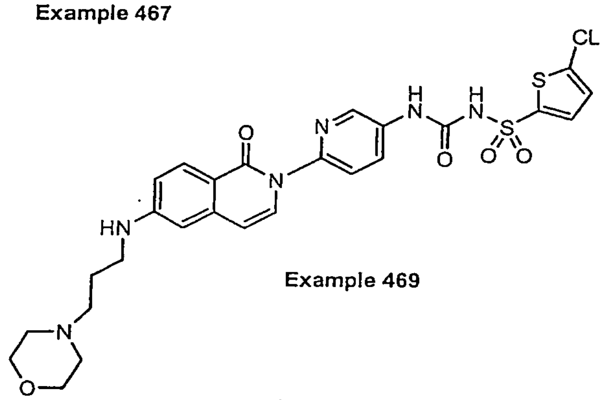

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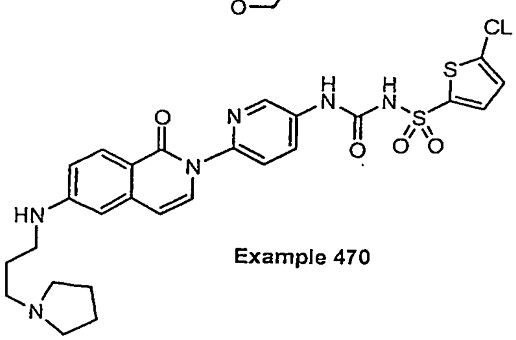
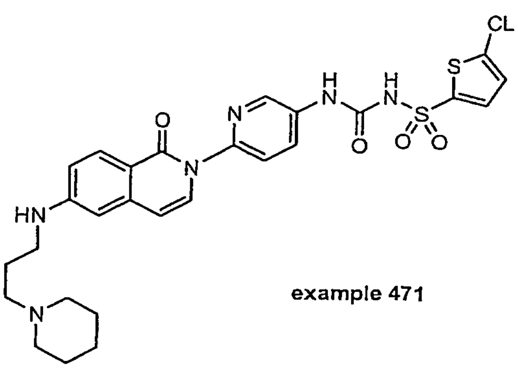
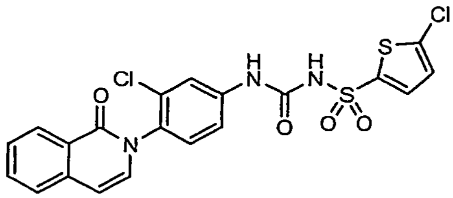


Example 470



example 471



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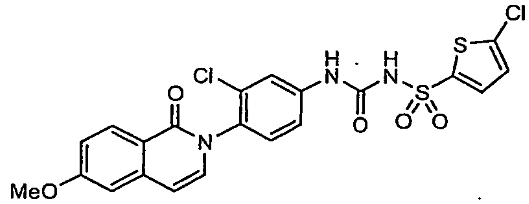
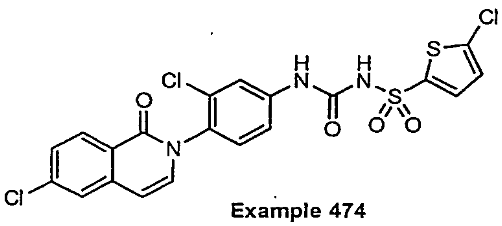
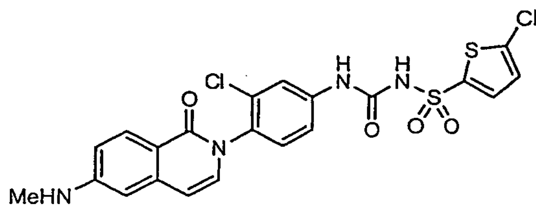


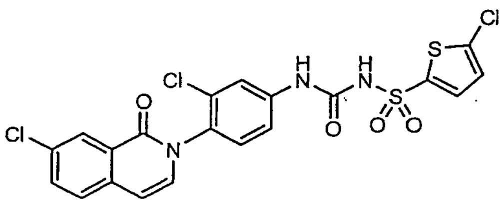
Example 473



Example 474



Example 475



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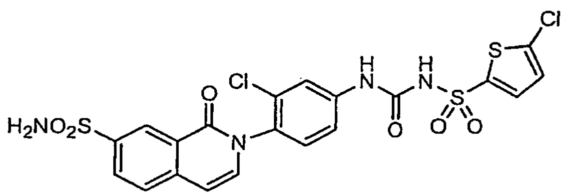

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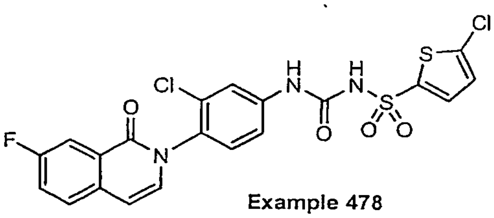

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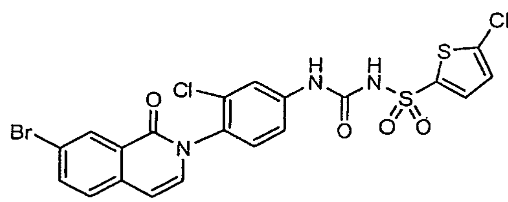
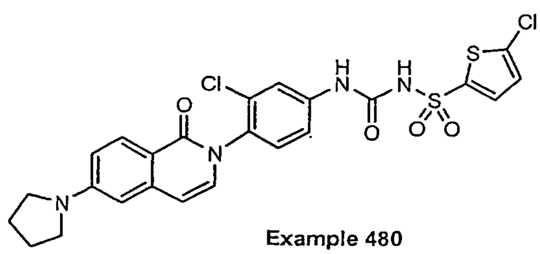
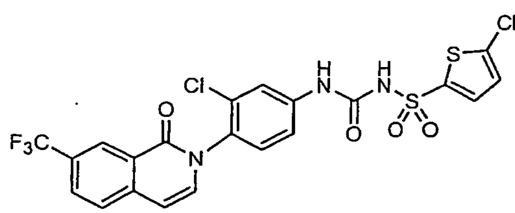


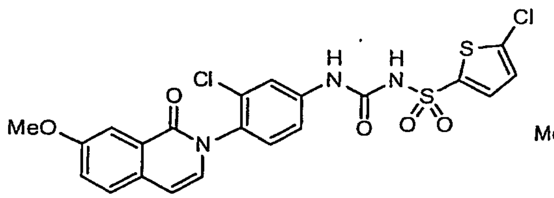
Example 479



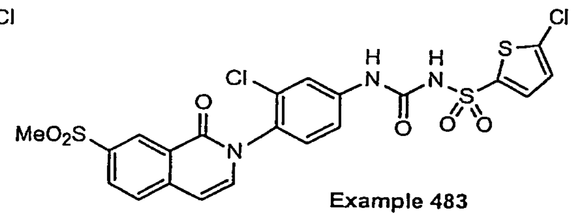
Example 480



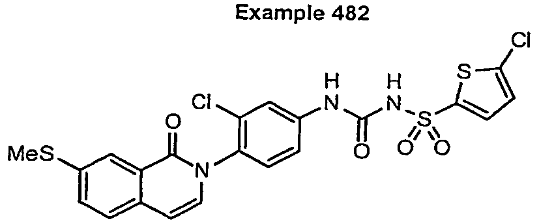
Example 481



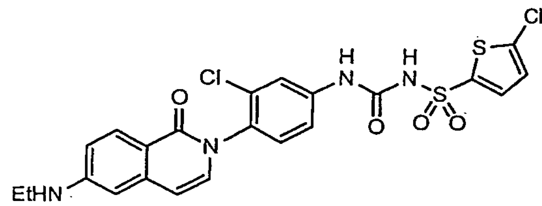
Example 482



Example 483



Example 484



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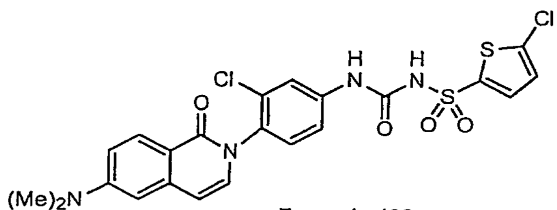
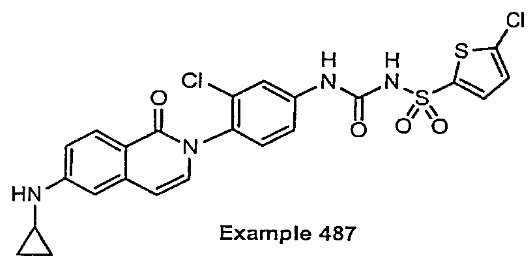
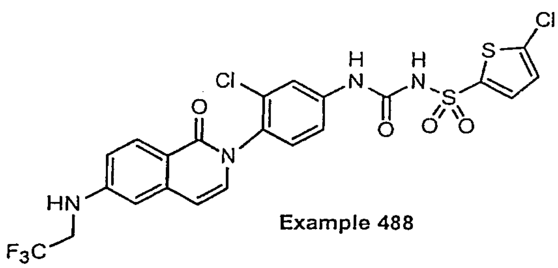


Example 486



Example 487



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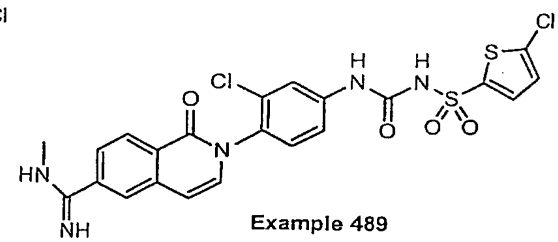
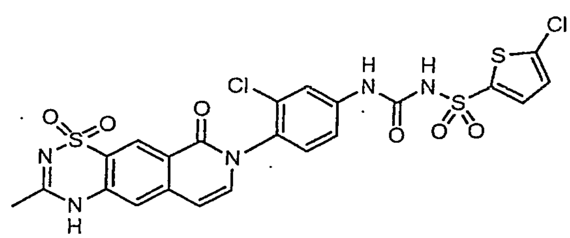
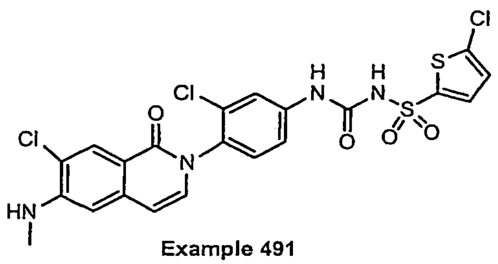


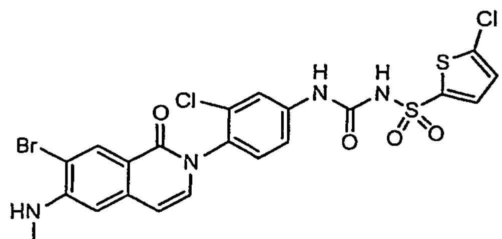
Example 489



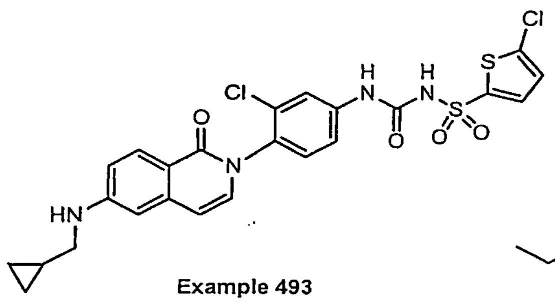
Example 490



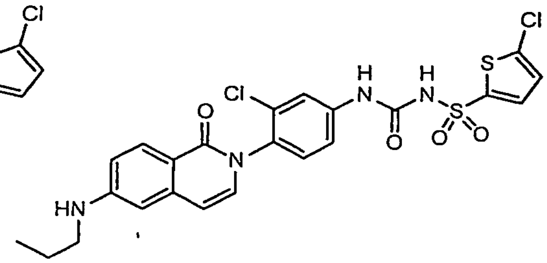
Example 491



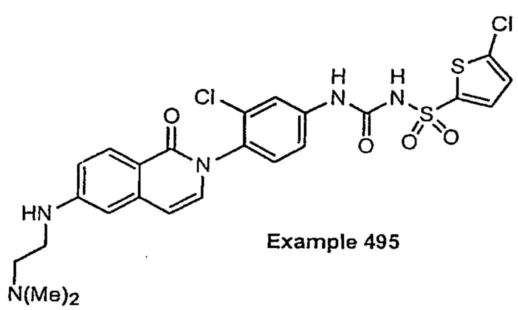
Example 492



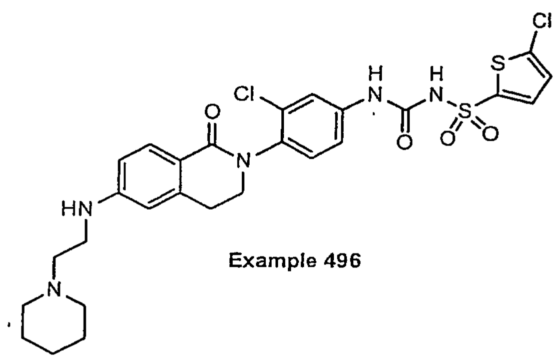
Example 493



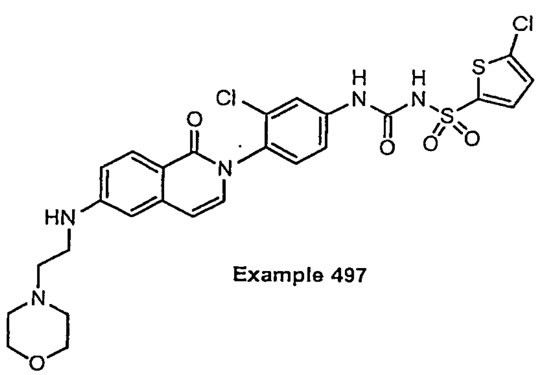
Example 494



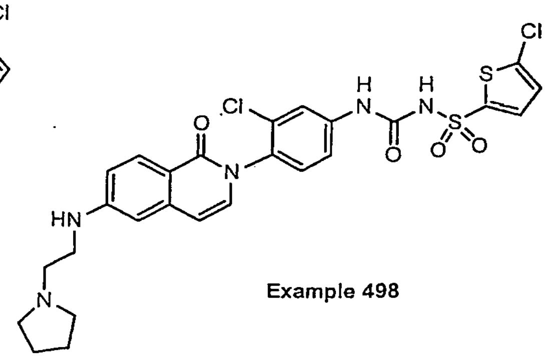
Example 495



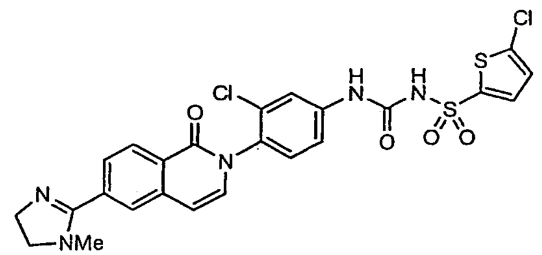
Example 496



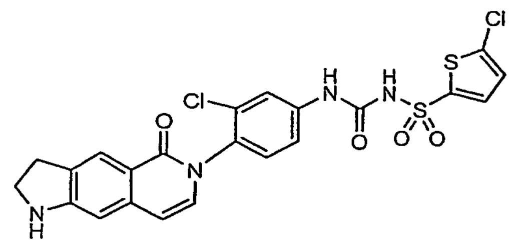
Example 497



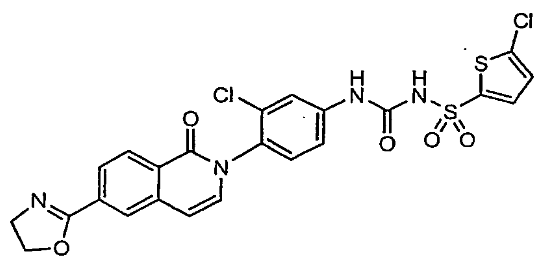
Example 498



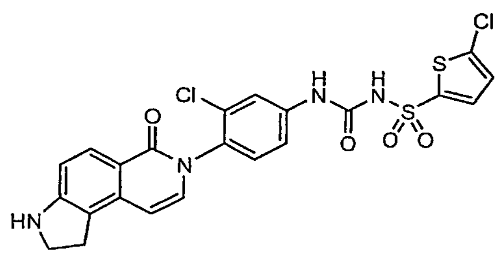
Example 499



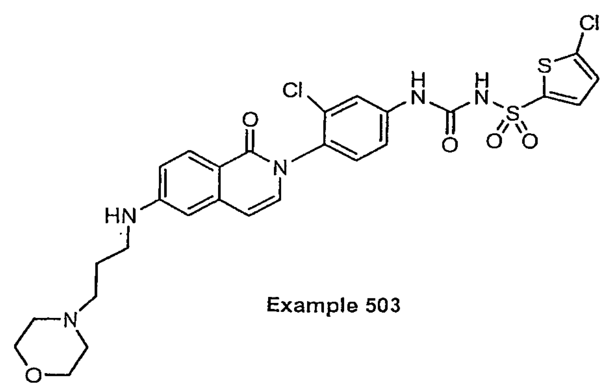
Example 500



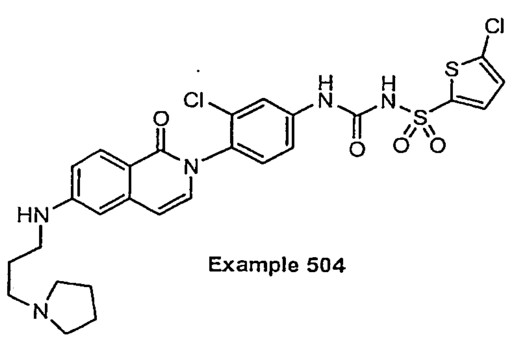
Example 501



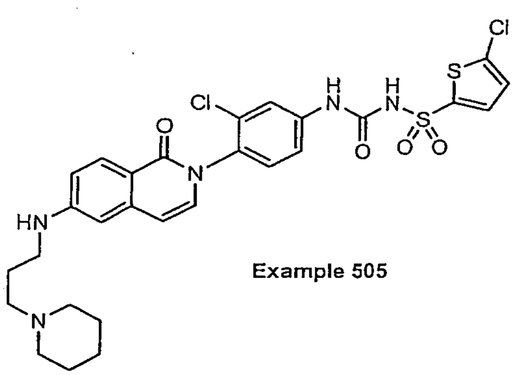
Example 502



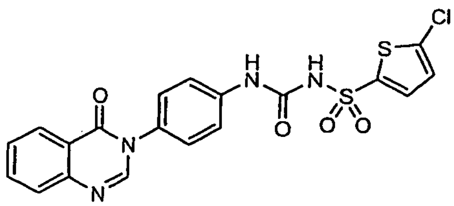
Example 503



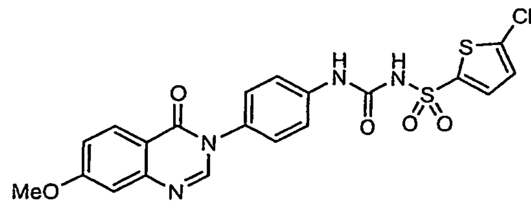
Example 504



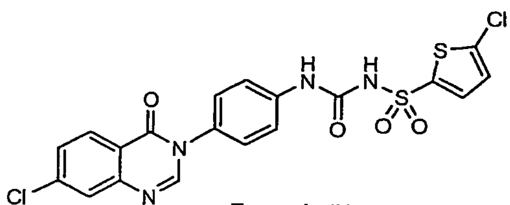
Example 505



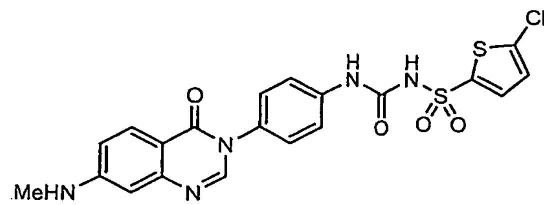
Example 506



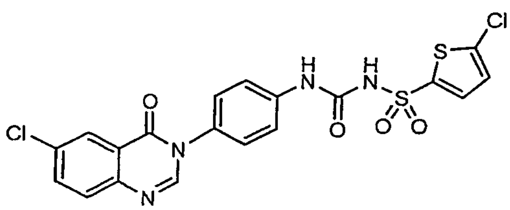
Example 507



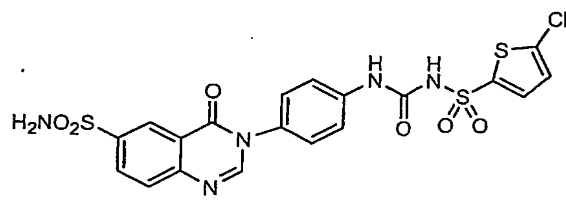
Example 508



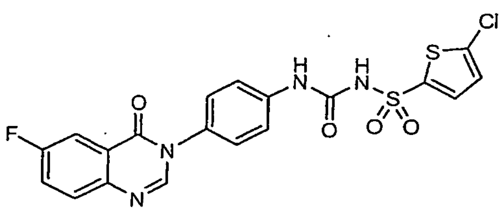
Example 509



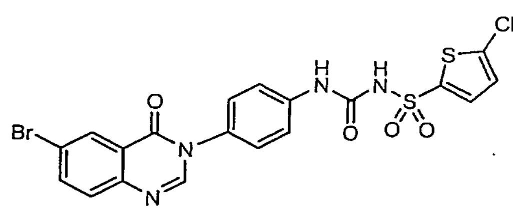
Example 510



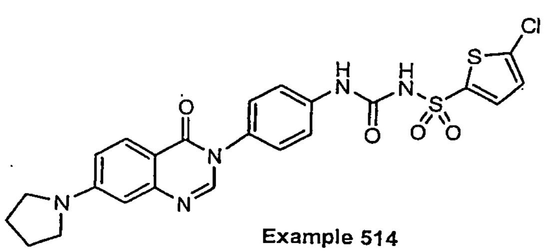
Example 511



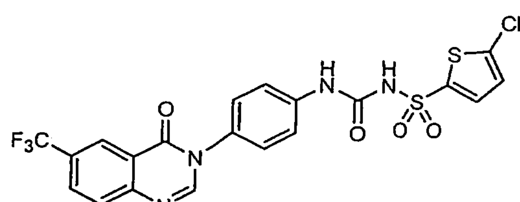
Example 512



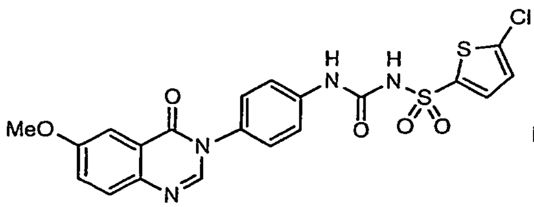
Example 513



Example 514



Example 515



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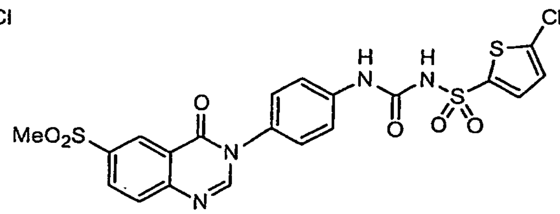

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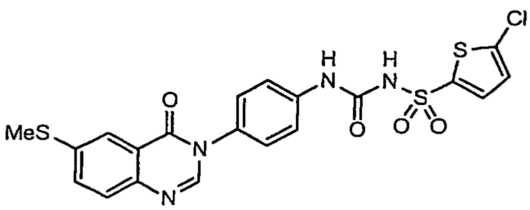

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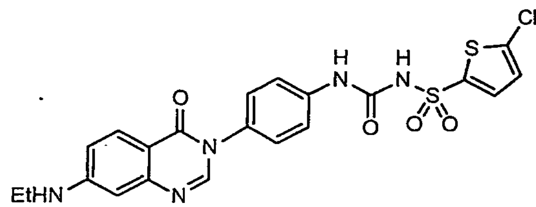

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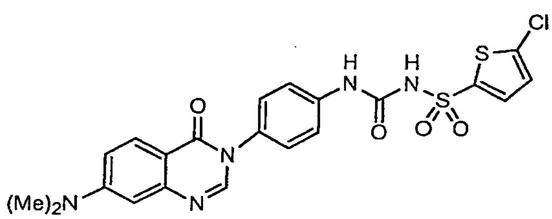

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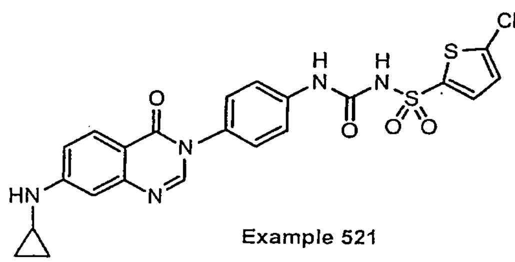

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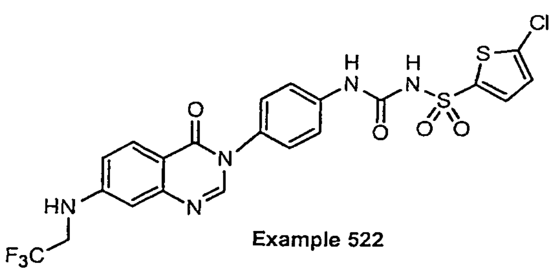

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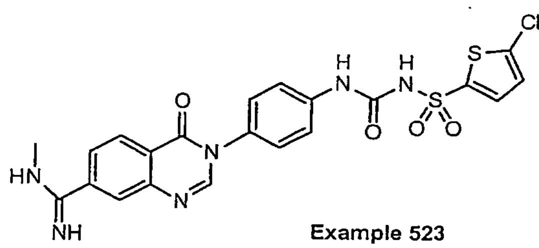

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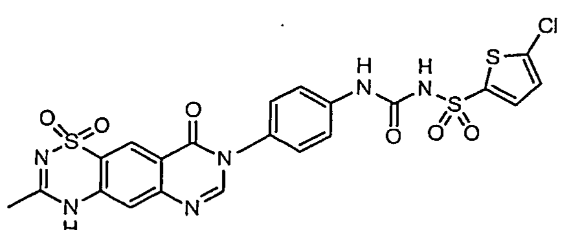

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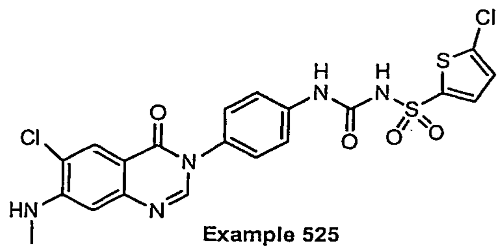

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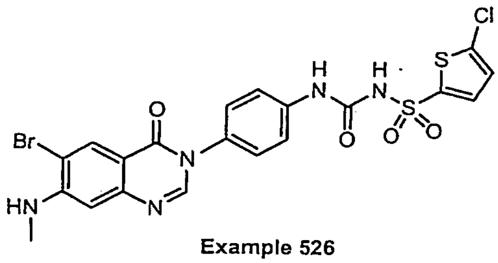

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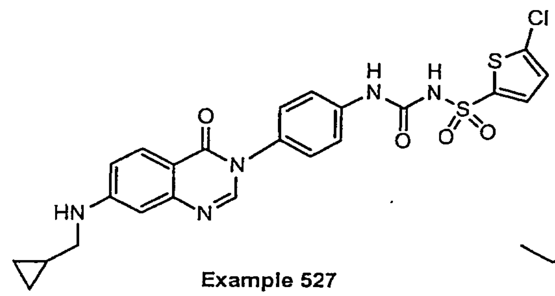

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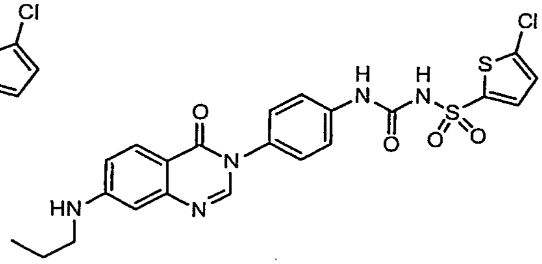

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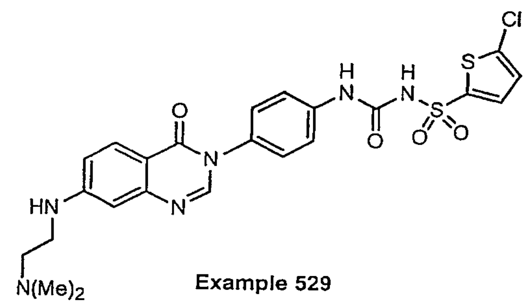

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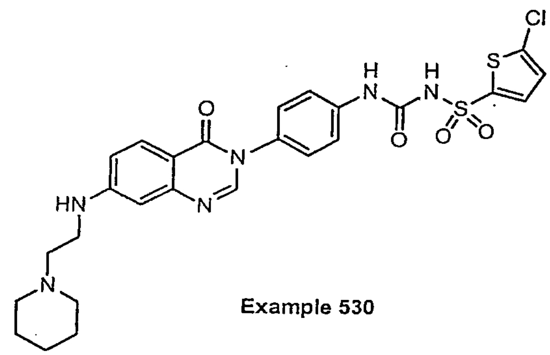

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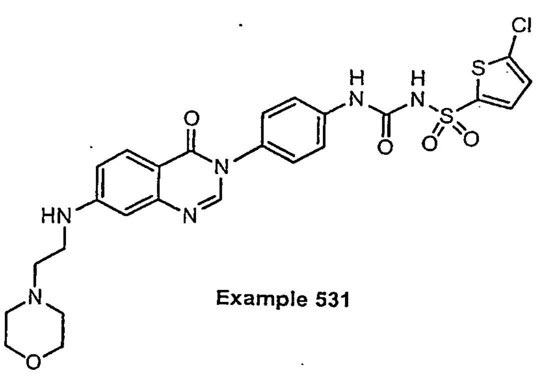

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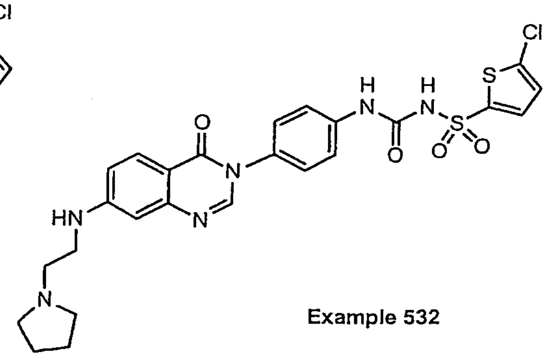

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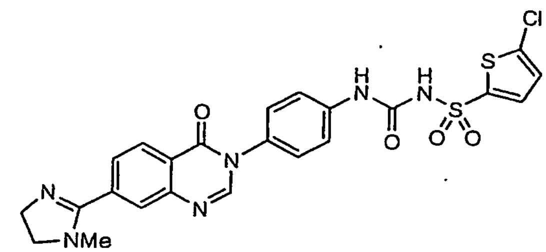

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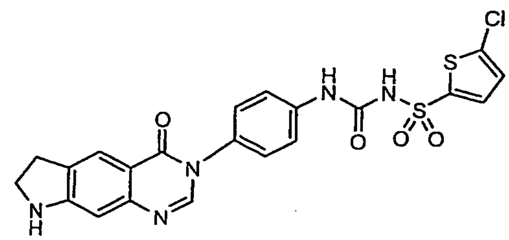

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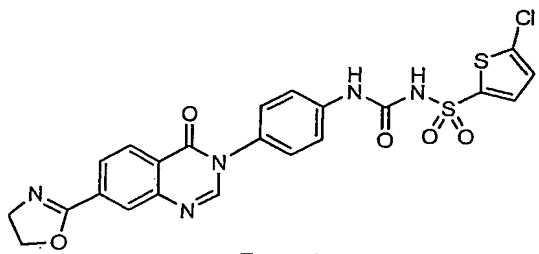

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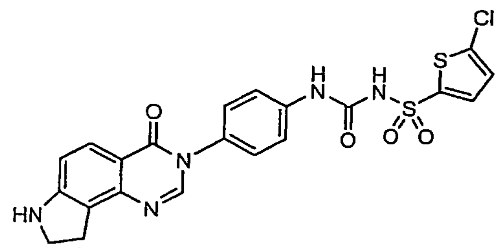

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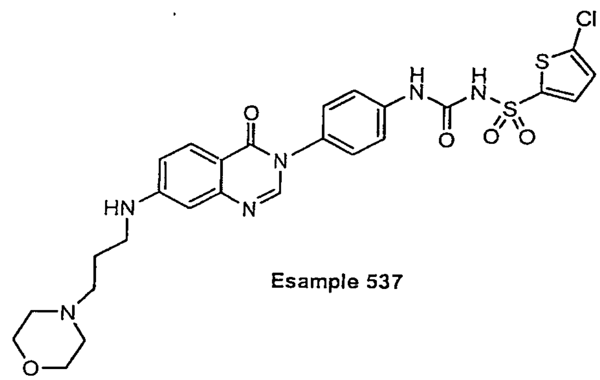

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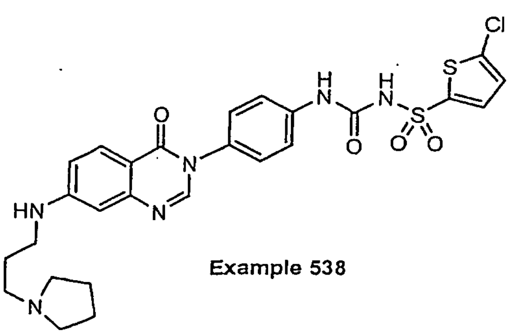

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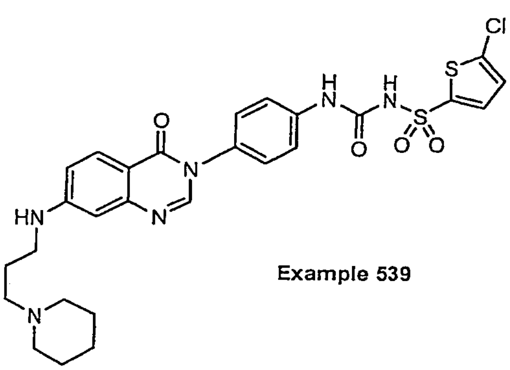

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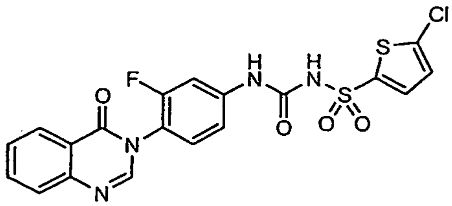

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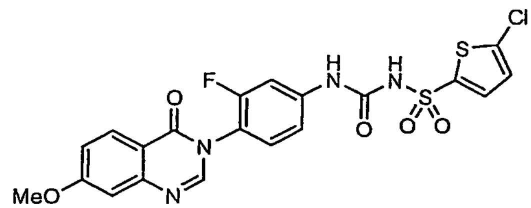

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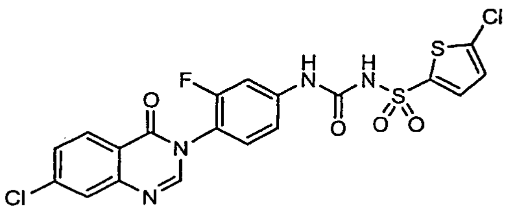

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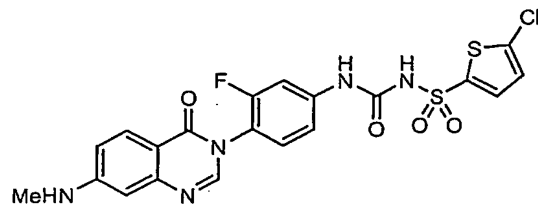

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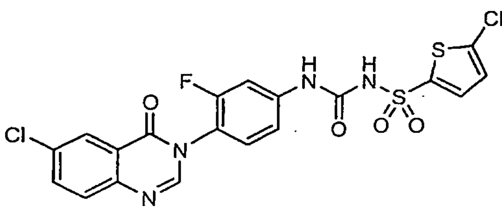

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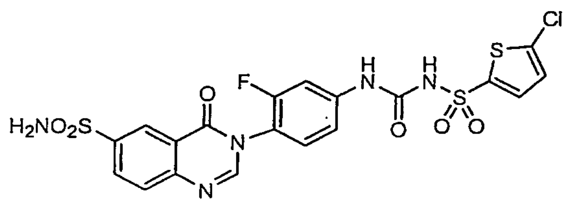

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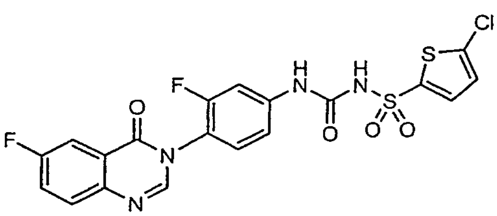

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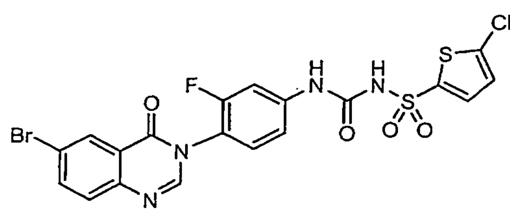

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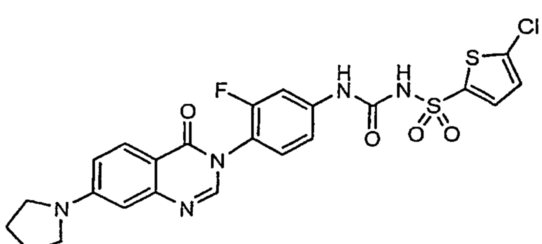

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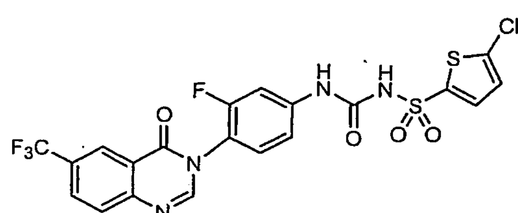

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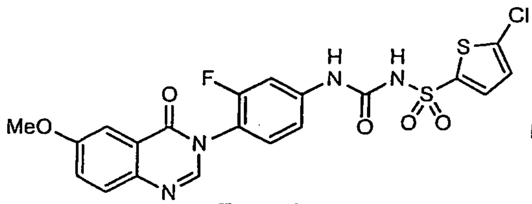

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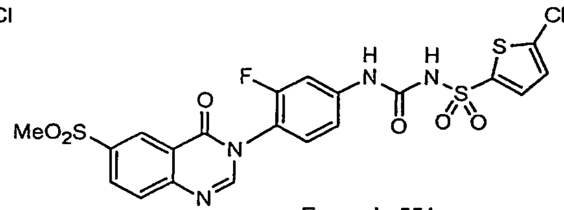

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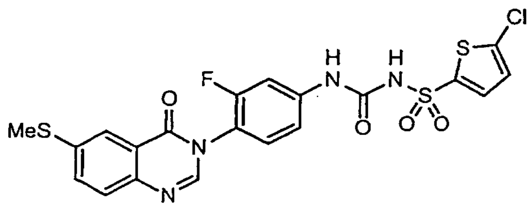

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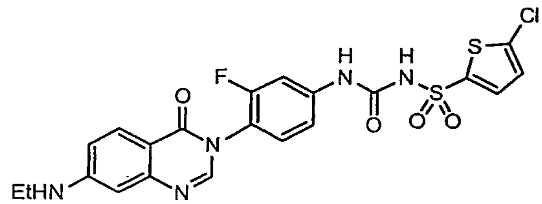

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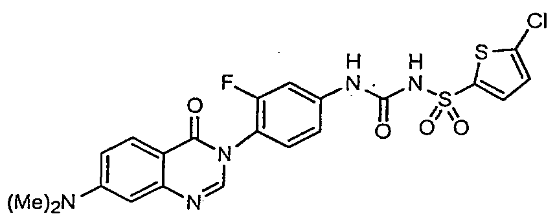

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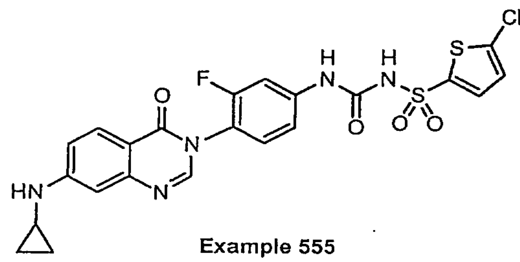

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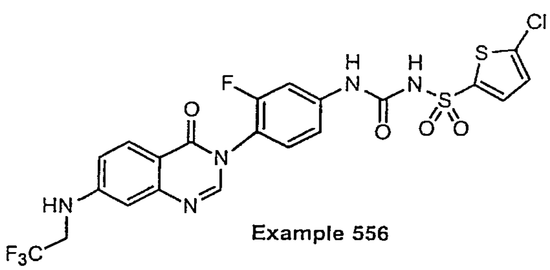

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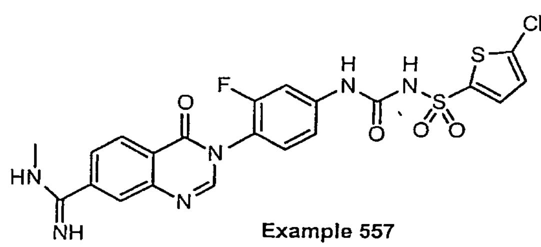

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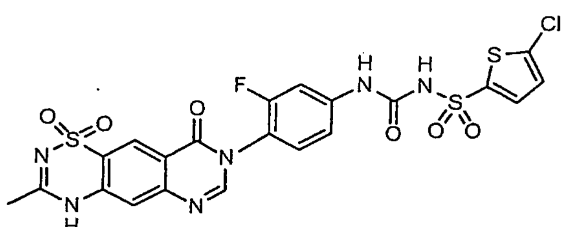

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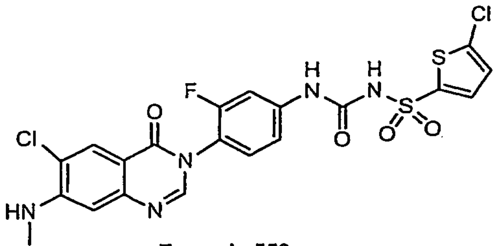

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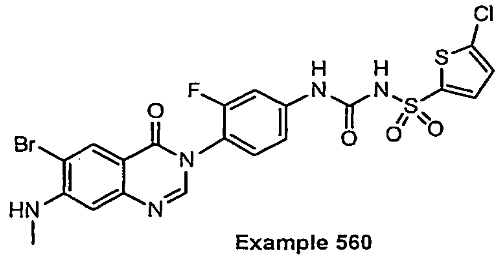
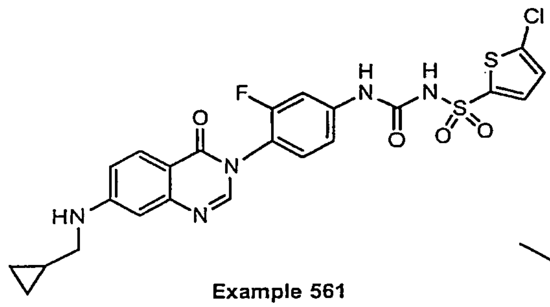


Example 560



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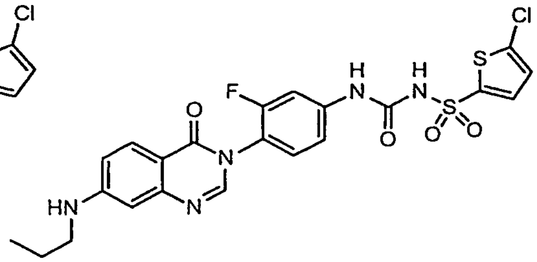

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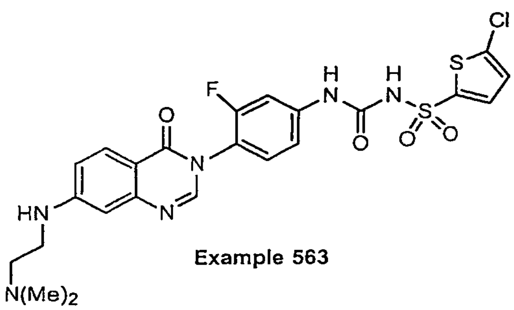

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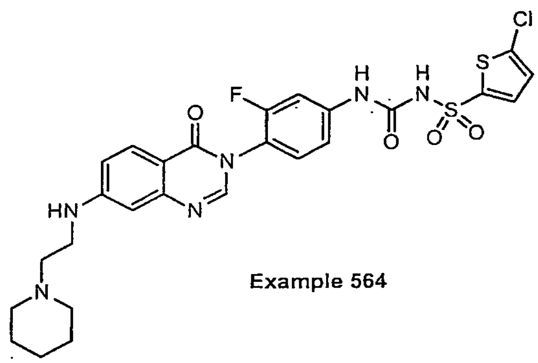

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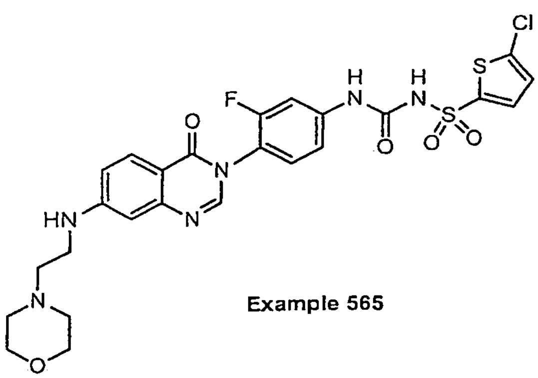

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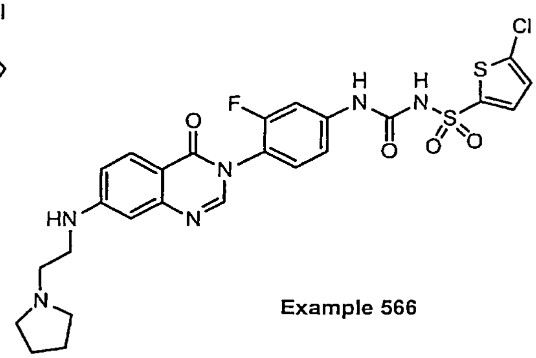

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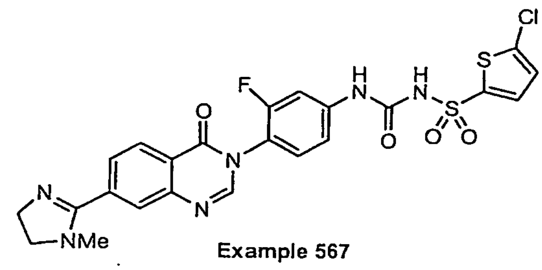

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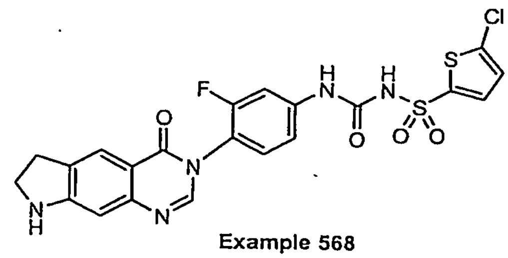
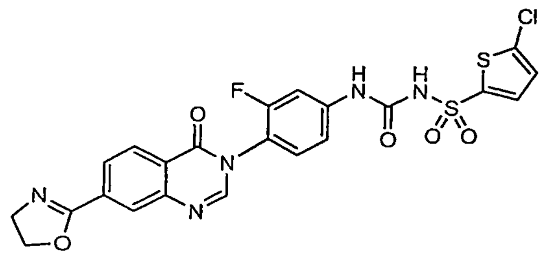


Example 568



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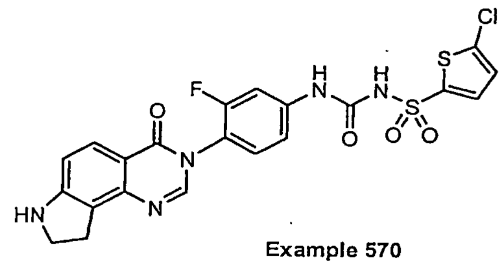

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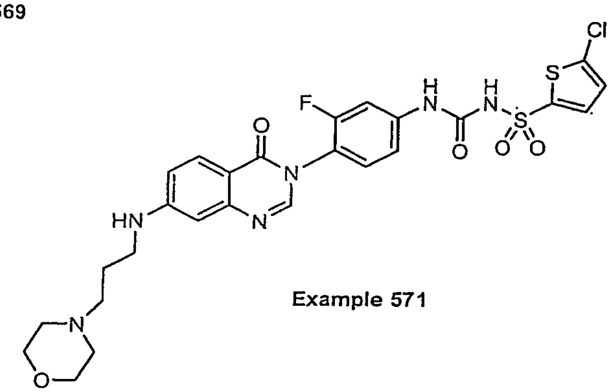

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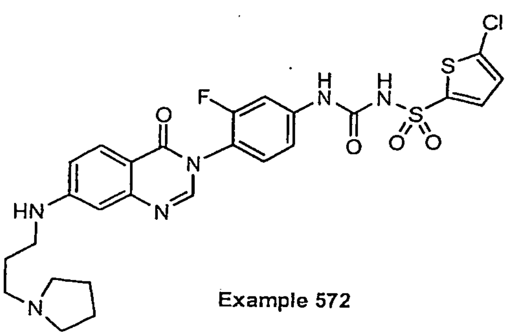

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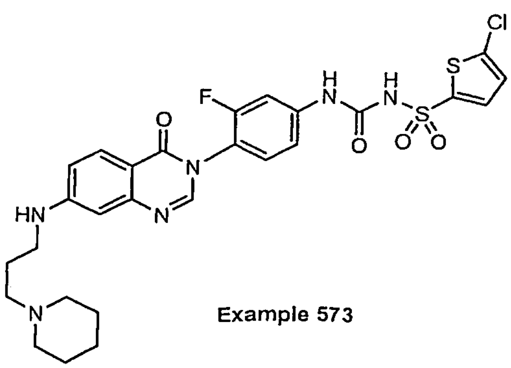

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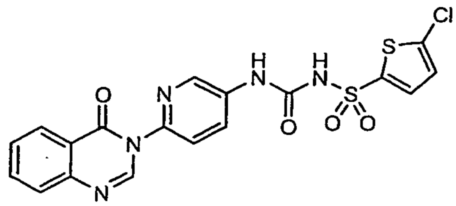

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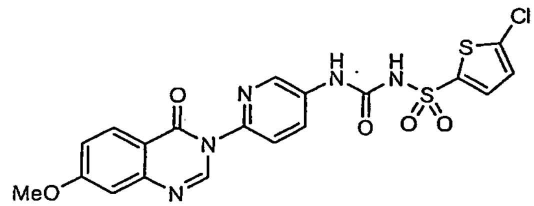

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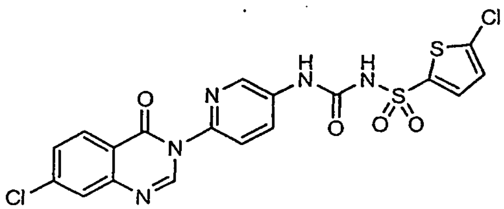

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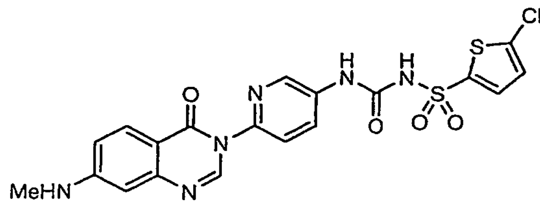

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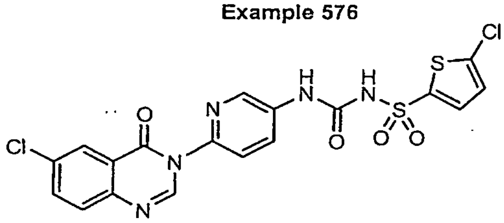

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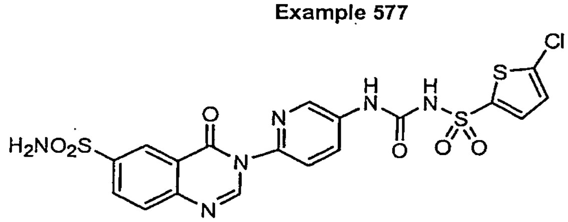

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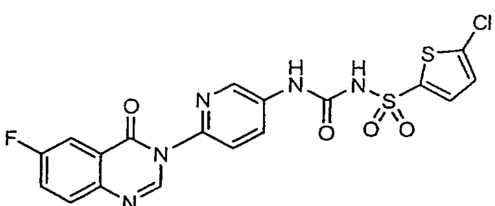

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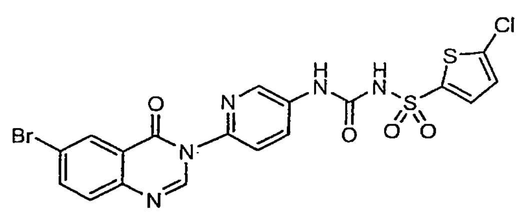

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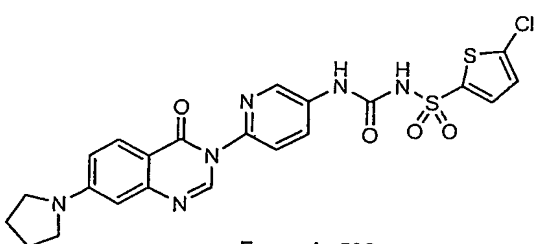

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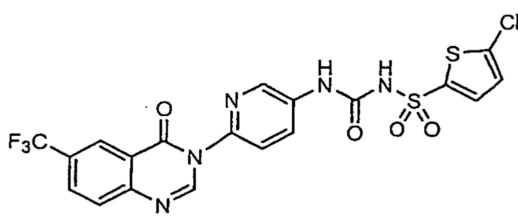

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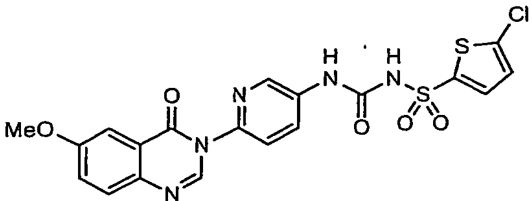

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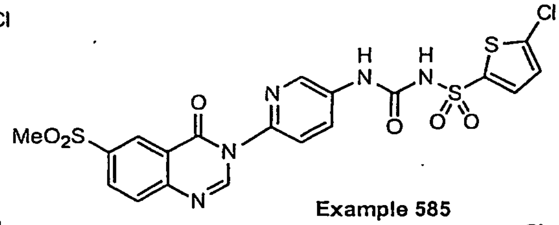

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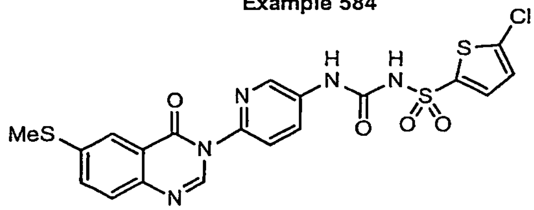

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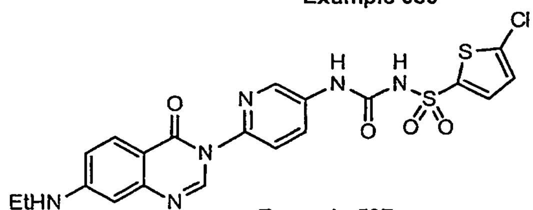

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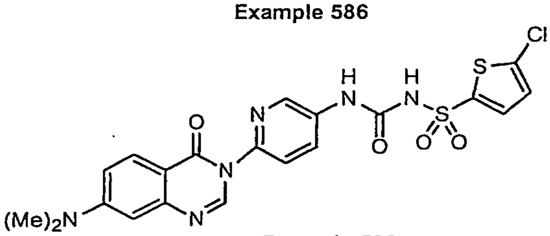

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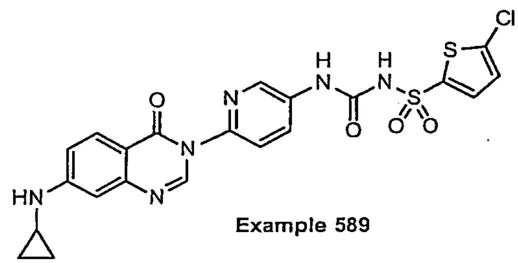
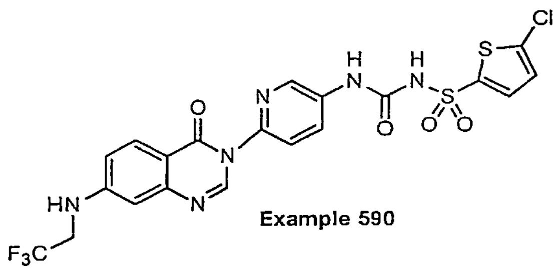
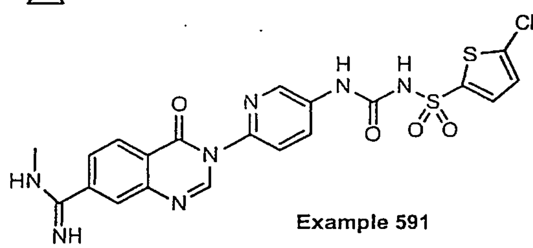


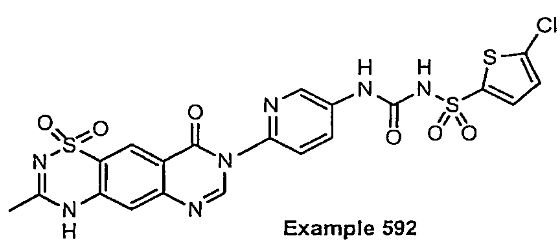
Example 589



Example 590



Example 591



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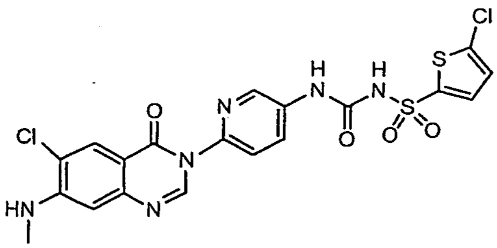

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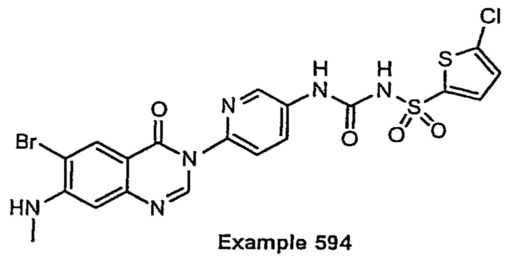
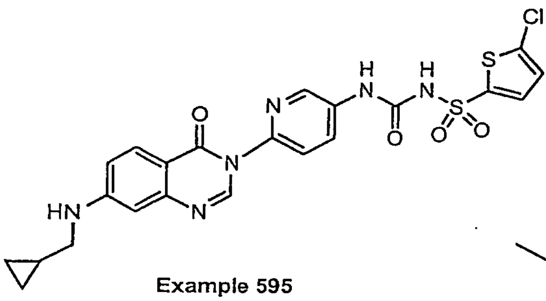


Example 594



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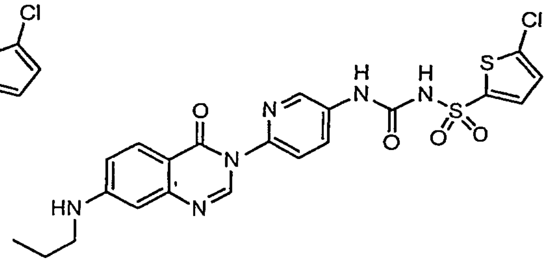
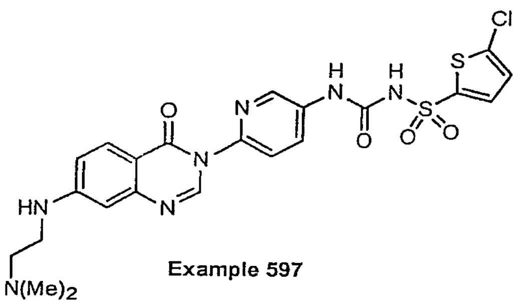


Example 596



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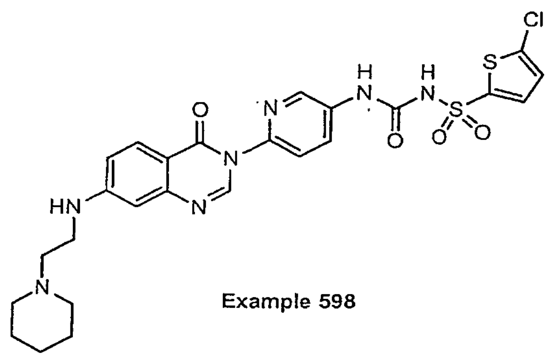

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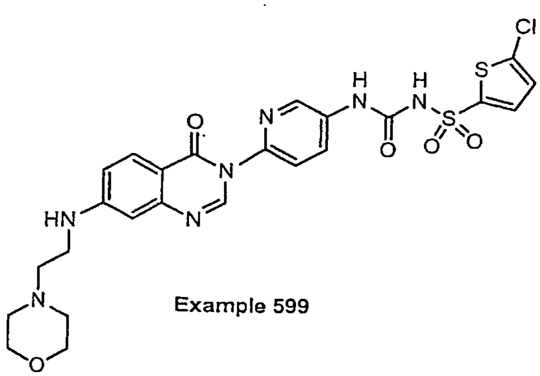

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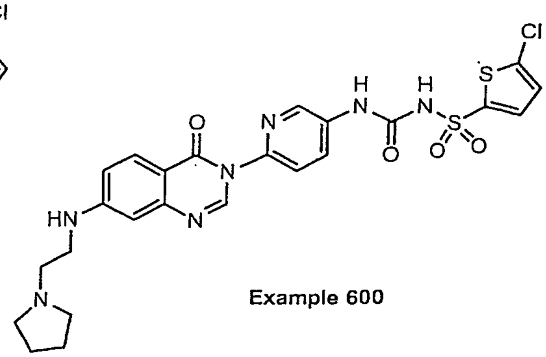

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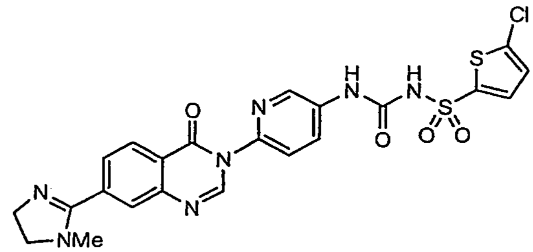

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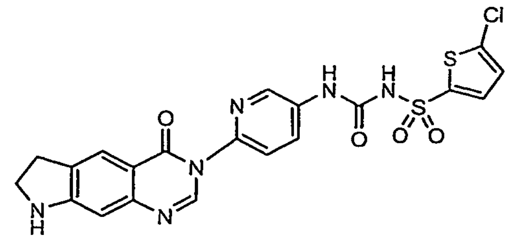
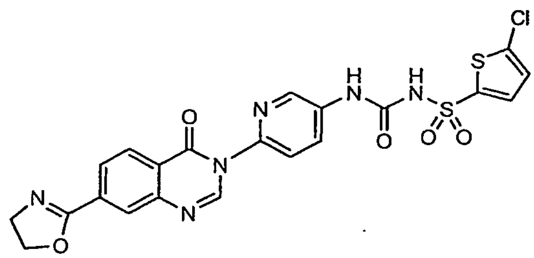
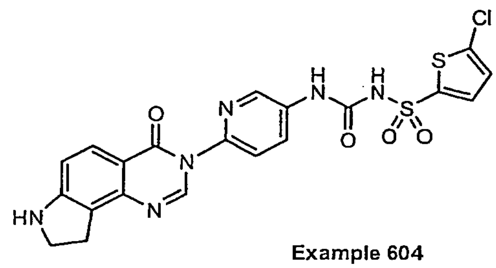


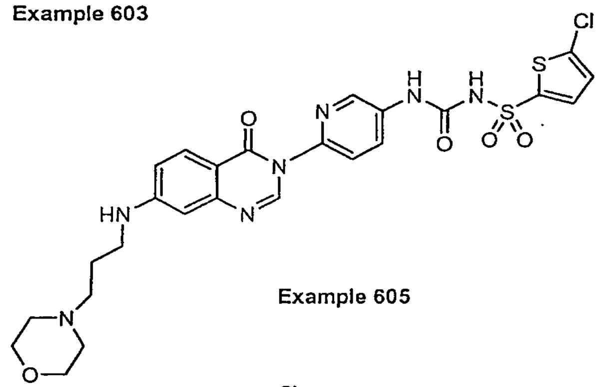
Example 602



Example 603



Example 604



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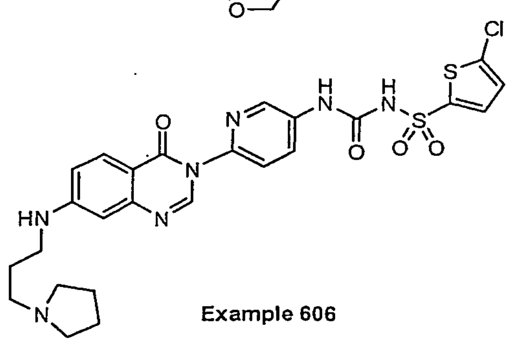

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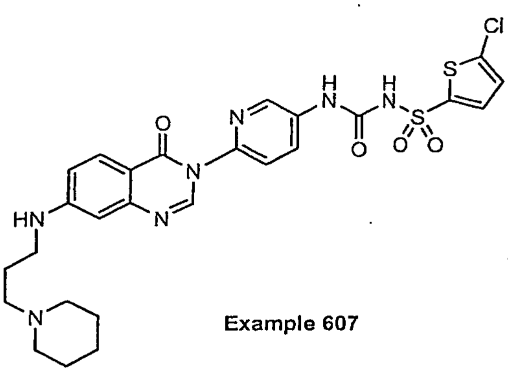
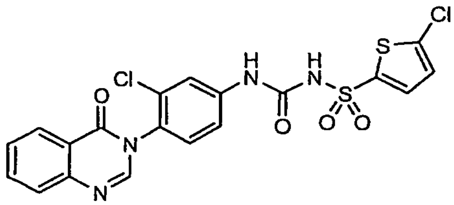
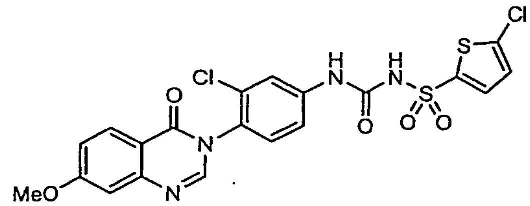


Example 607



Example 608



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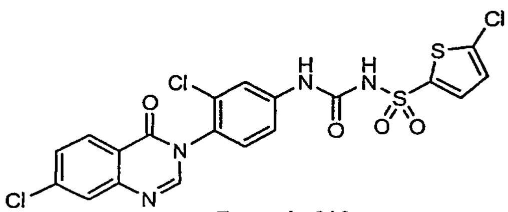
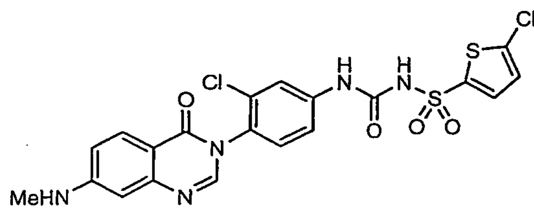
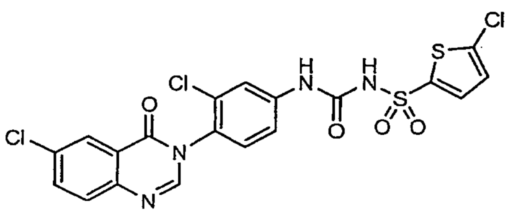


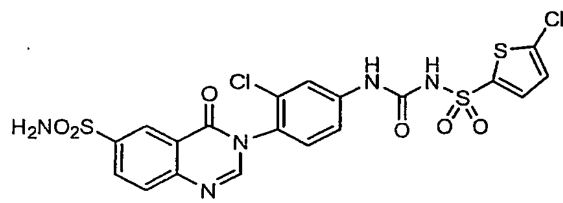
Example 610



Example 611



Example 612



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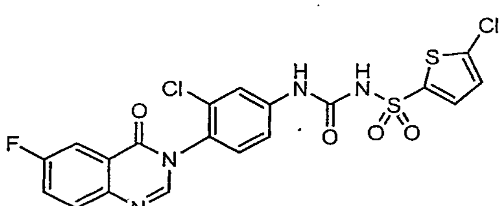
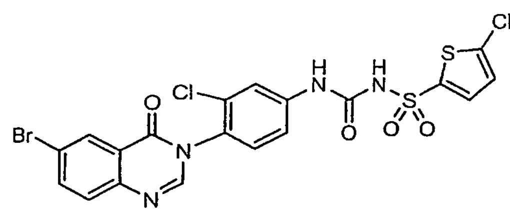
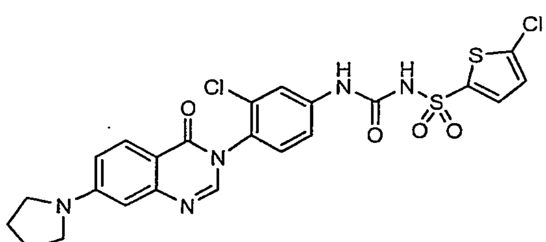


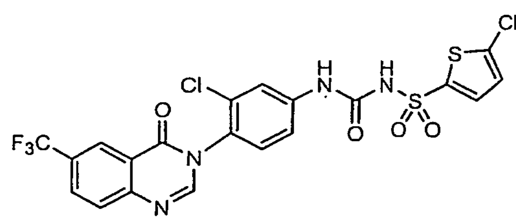
Example 614



Example 615



Example 616



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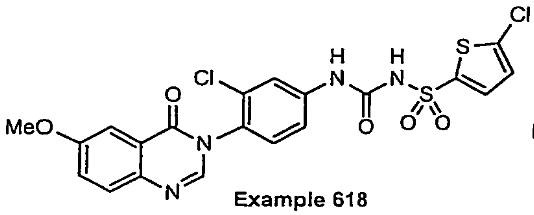

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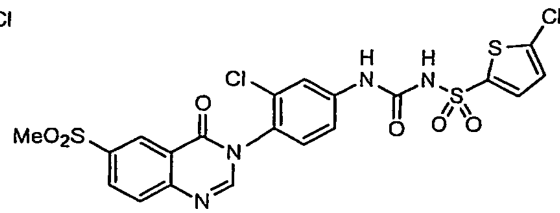
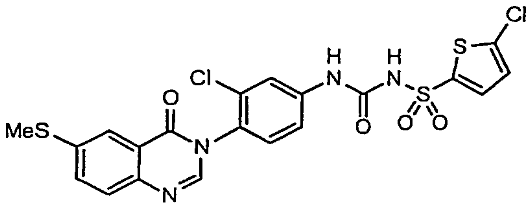
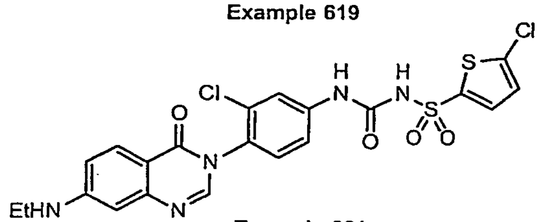


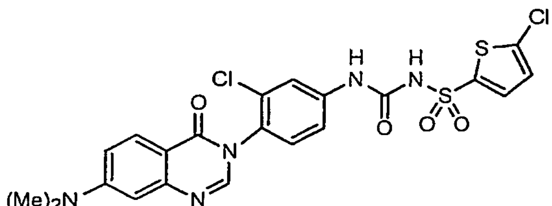
Example 619



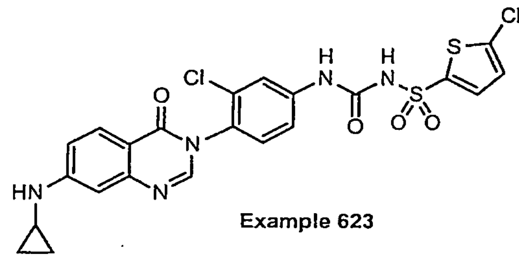
Example 620



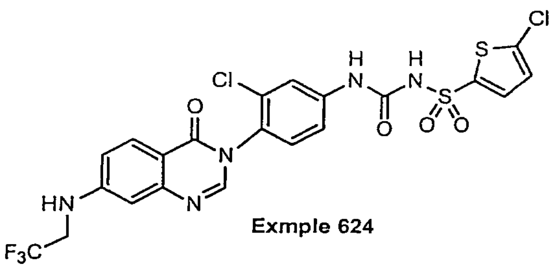
Example 621



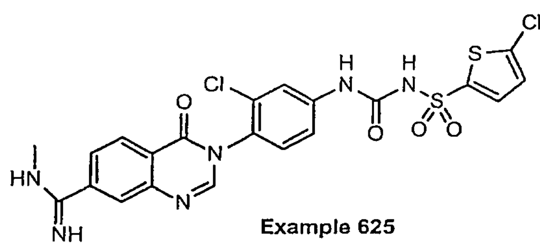
Example 622



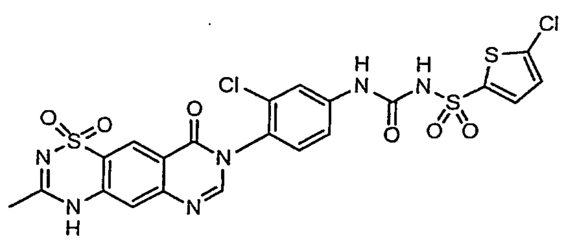
Example 623



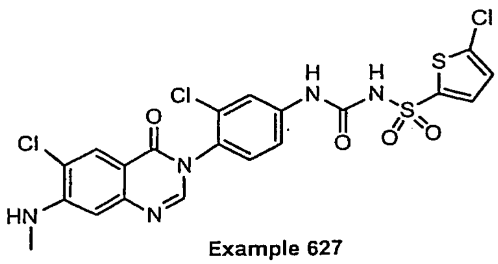
Exmple 624



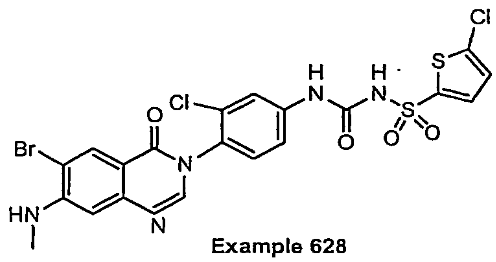
Example 625



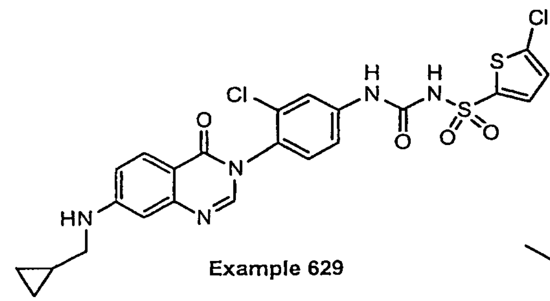
Example 626



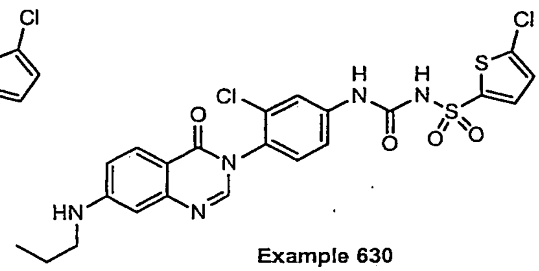
Example 627



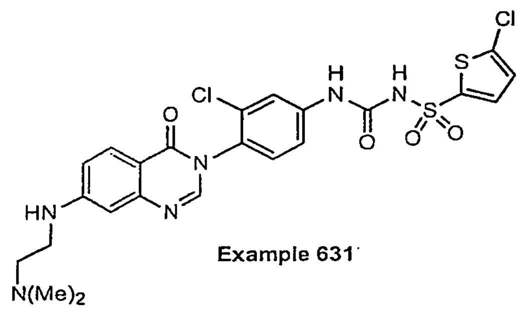
Example 628



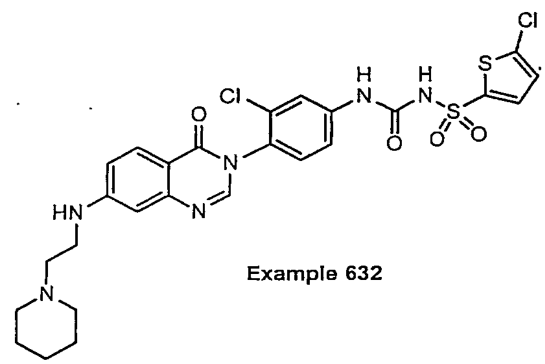
Example 629



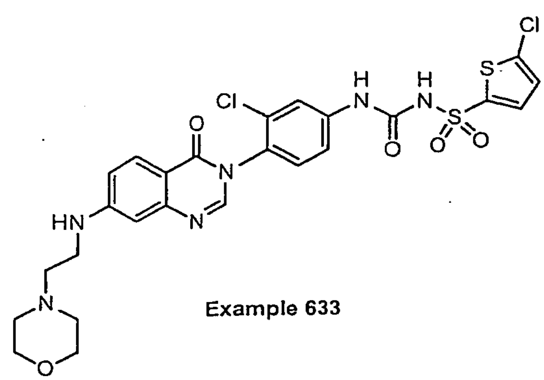
Example 630



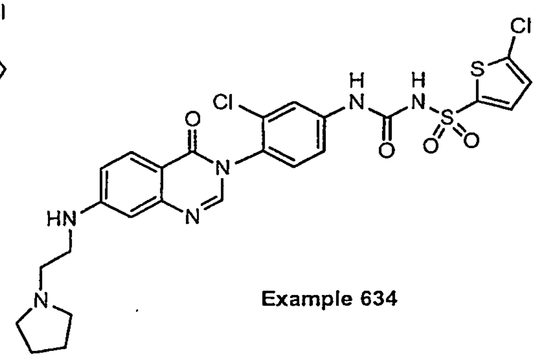
Example 631



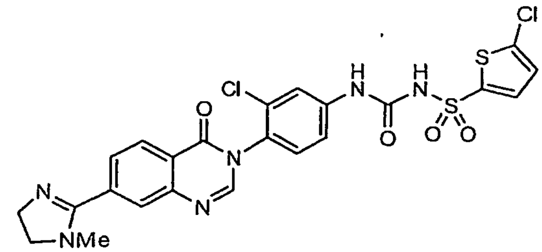
Example 632



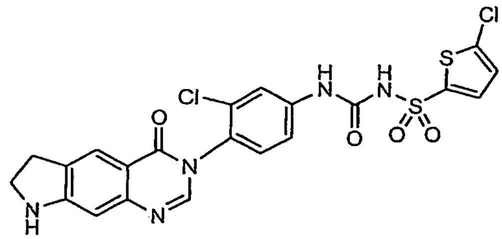
Example 633



Example 634



Example 635



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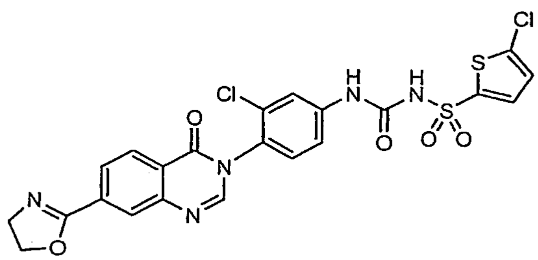

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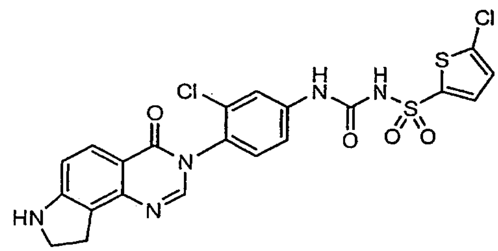
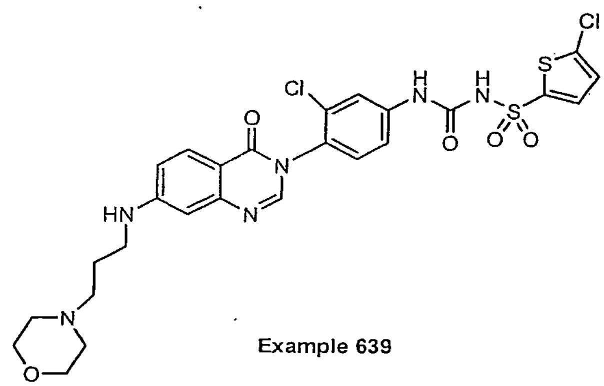
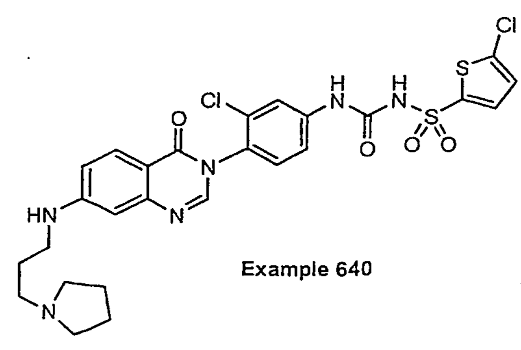


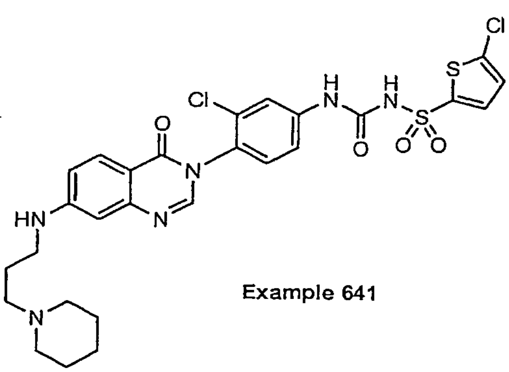
Example 638



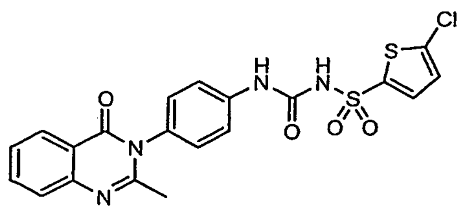
Example 639



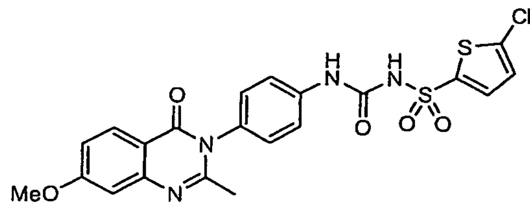
Example 640



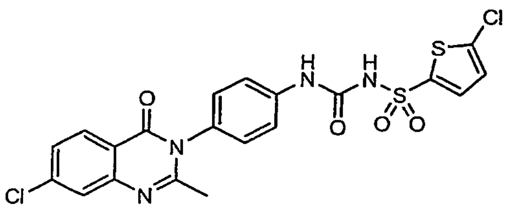
Example 641



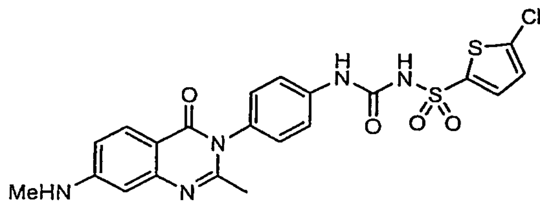
Example 642



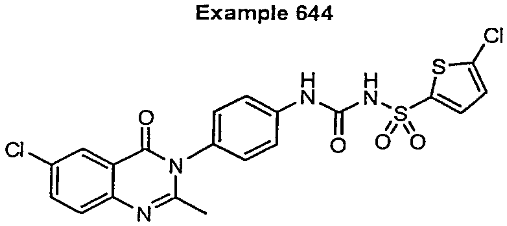
Example 643



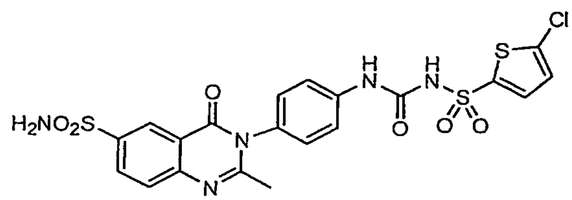
Example 644



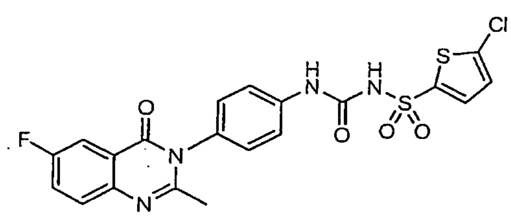
Example 645



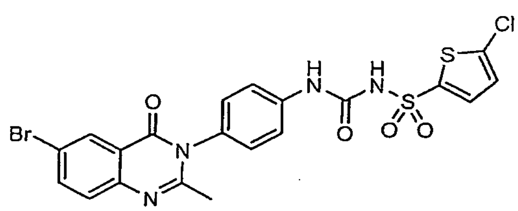
Example 646



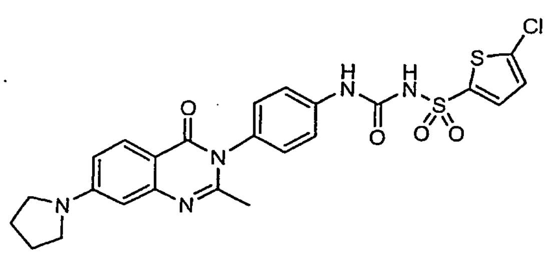
Example 647



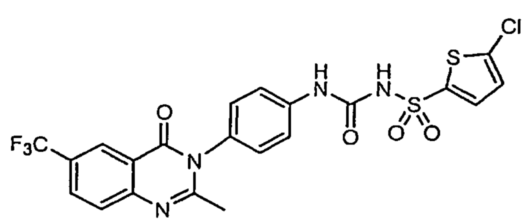
Example 648



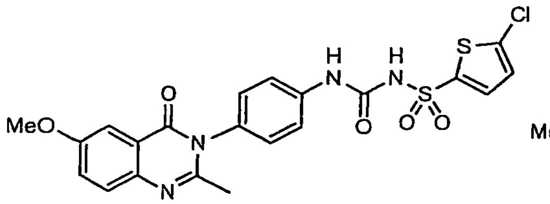
Example 649



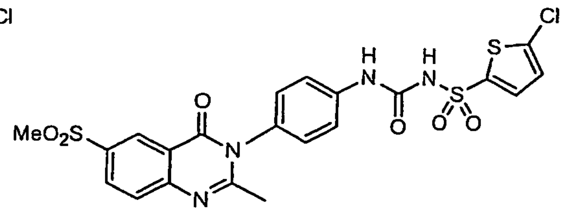
Example 650



Example 651



Example 652



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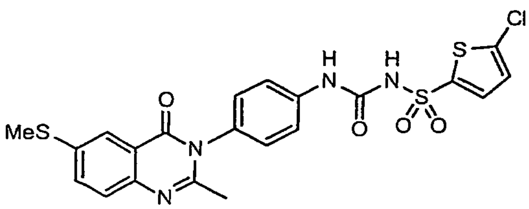
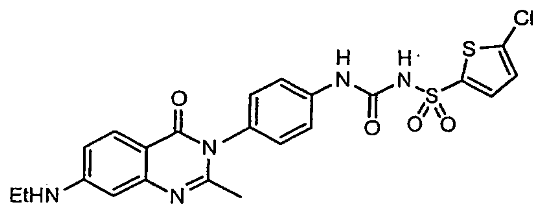
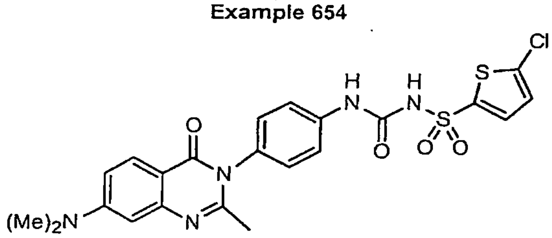


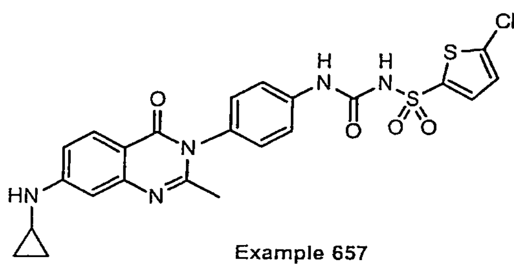
Example 654



Example 655



Example 656



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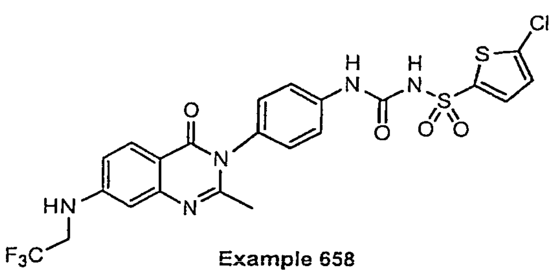

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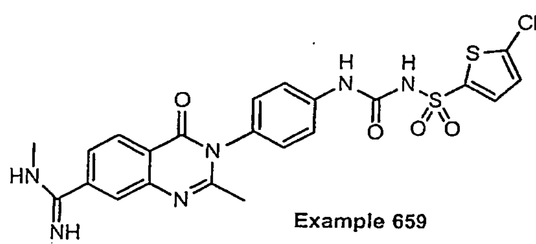
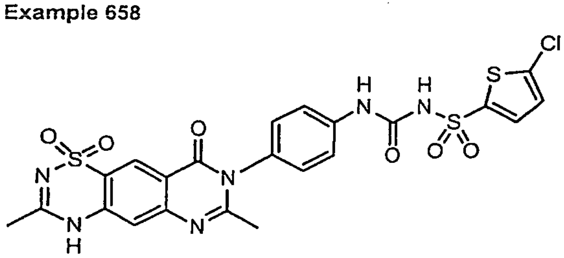
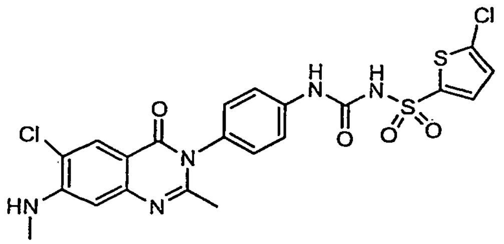


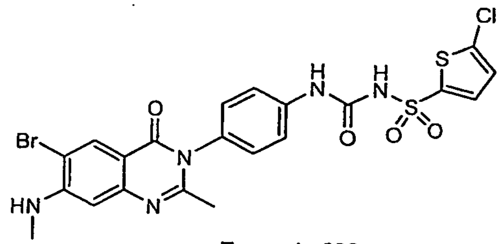
Example 659



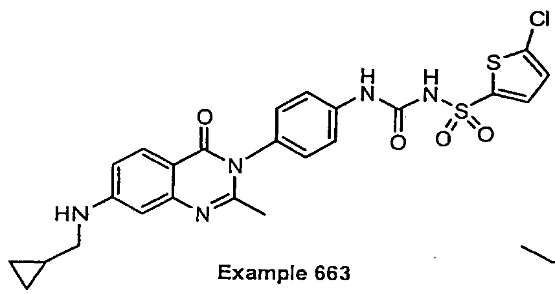
Example 660



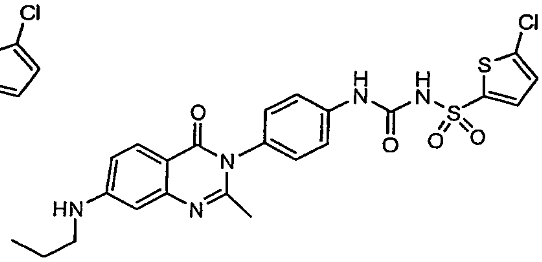
Example 661



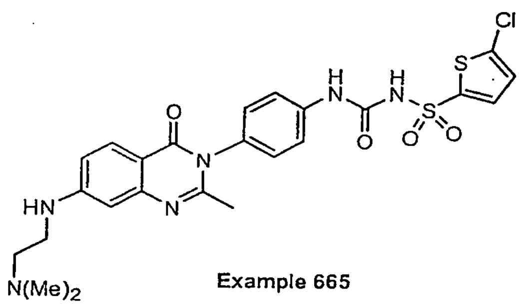
Example 662



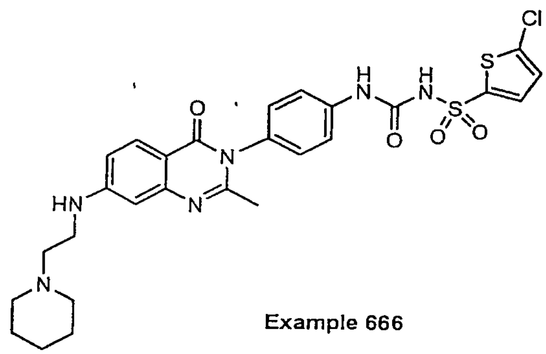
Example 663



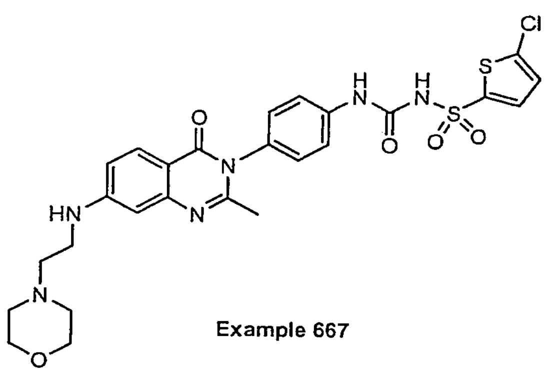
Example 664



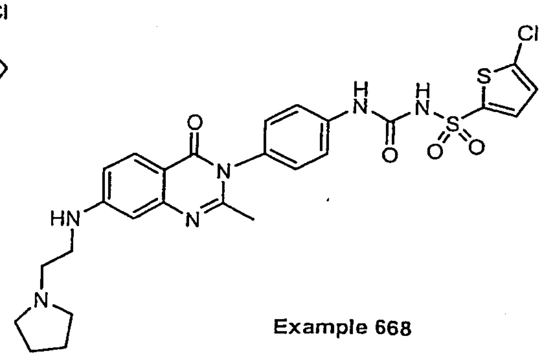
Example 665



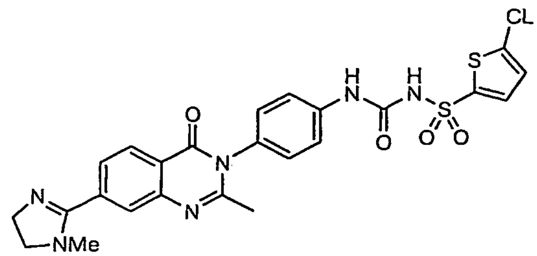
Example 666



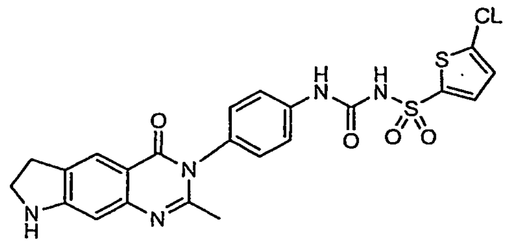
Example 667



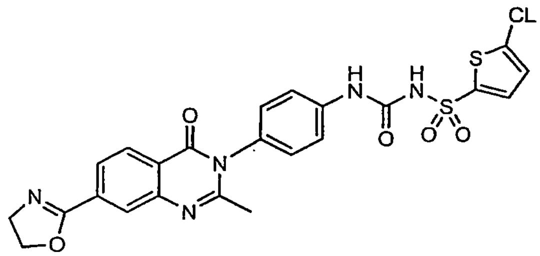
Example 668



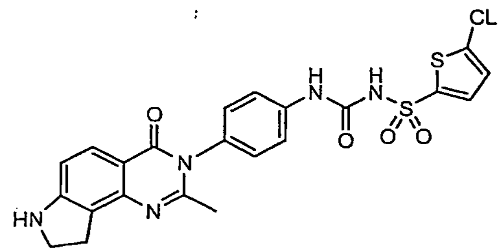
Example 669



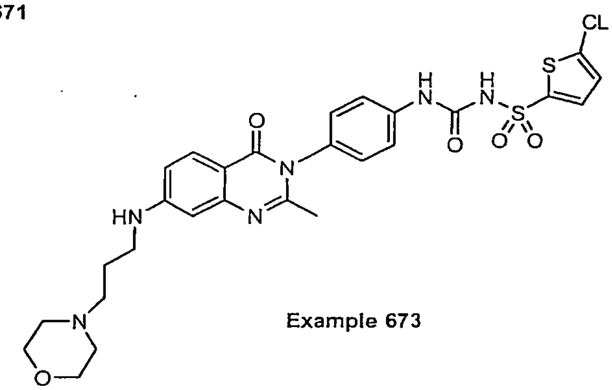
Example 670



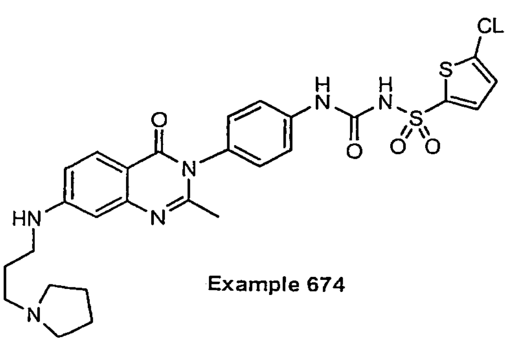
Example 671



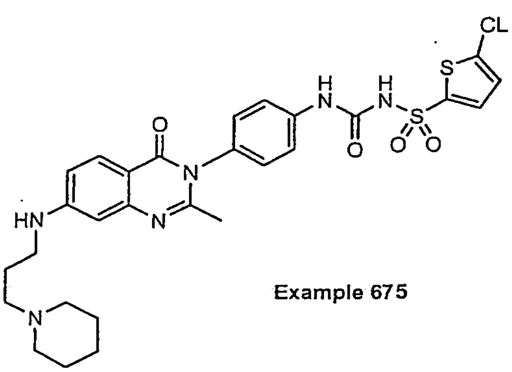
Example 672



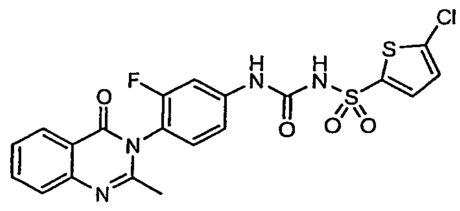
Example 673



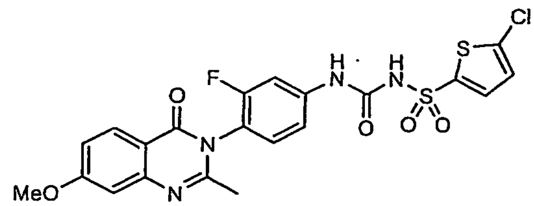
Example 674



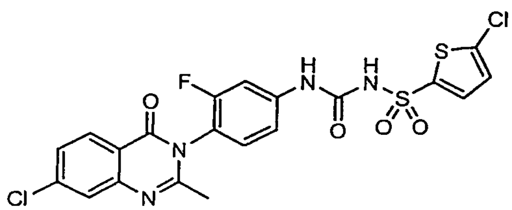
Example 675



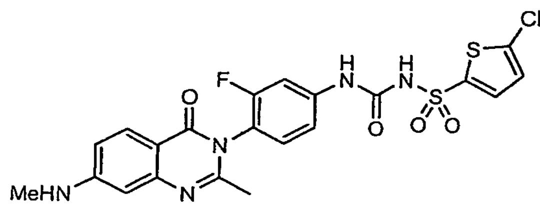
Example 676



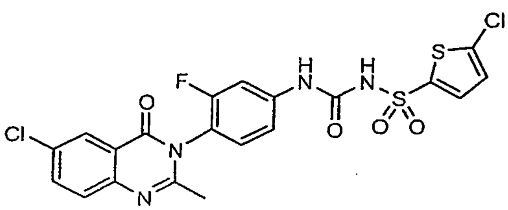
Example 677



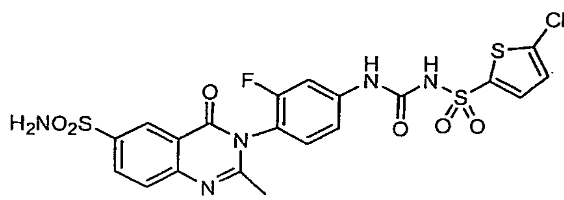
Example 678



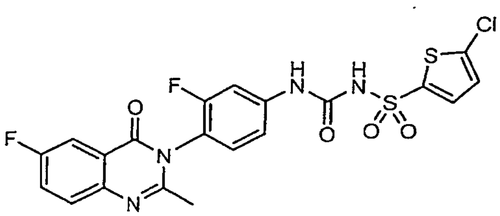
Example 679



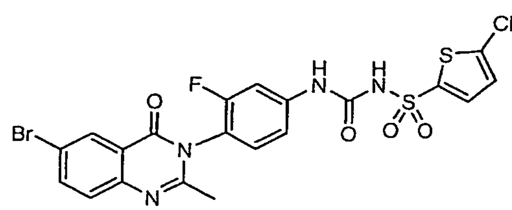
Example 680



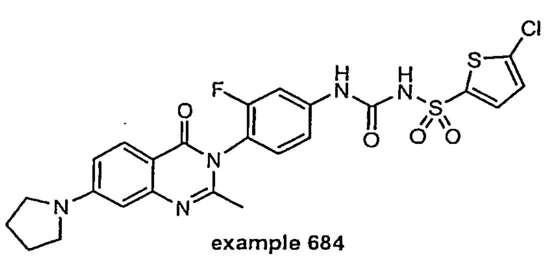
Example 681



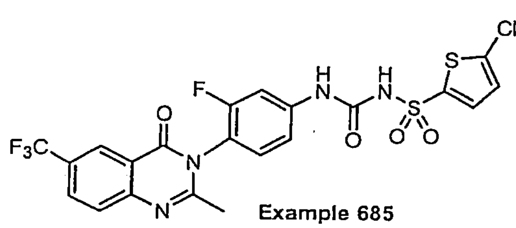
Exmple 682



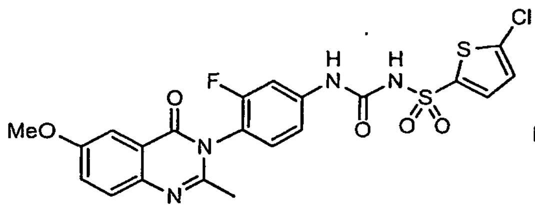
Example 683



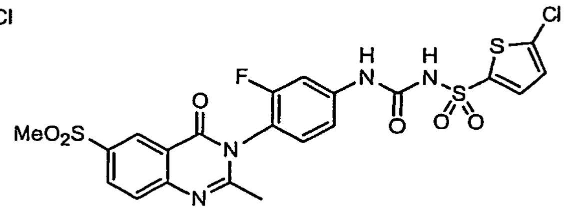
example 684



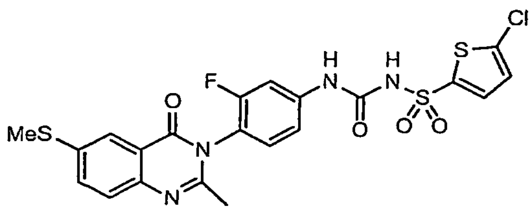
Example 685



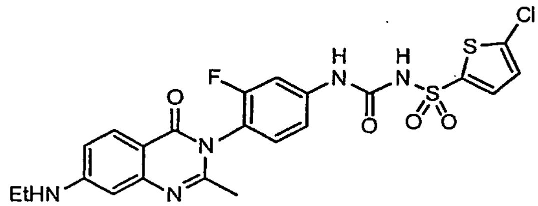
Example 686



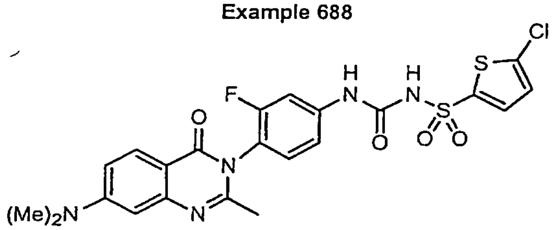
Example 687



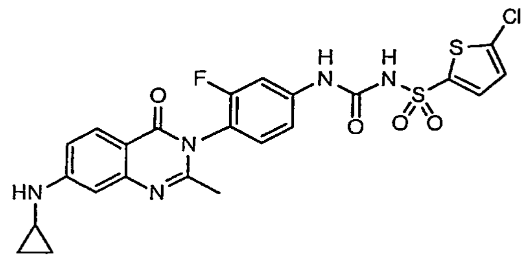
Example 688



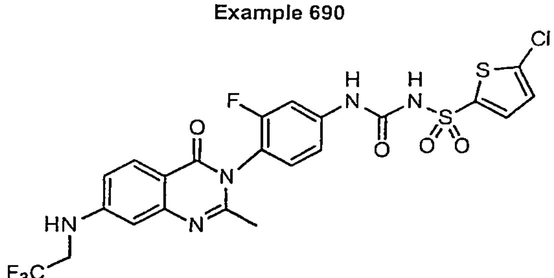
Example 689



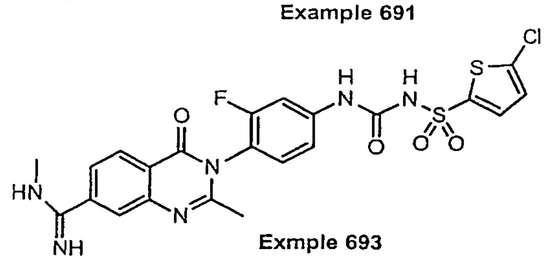
Example 690



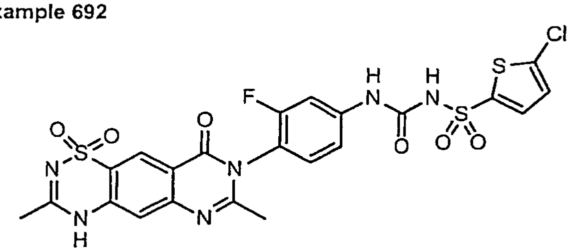
Example 691



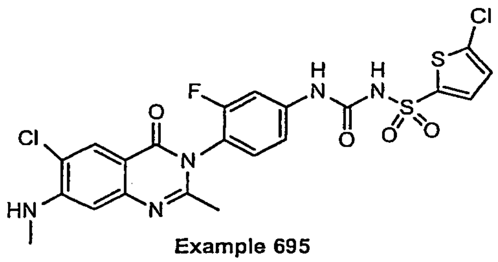
Example 692



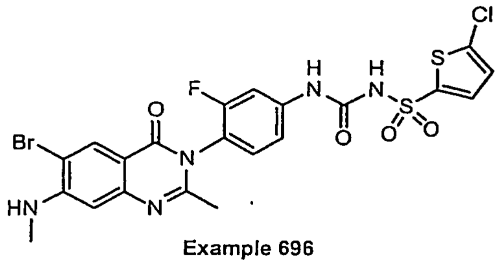
Exmple 693



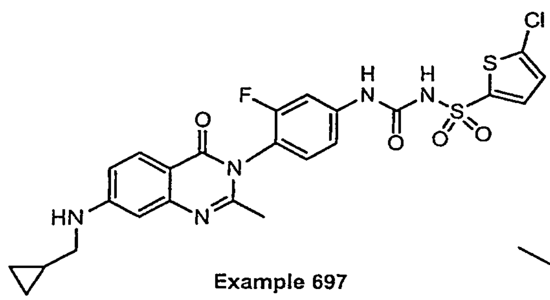
Example 694



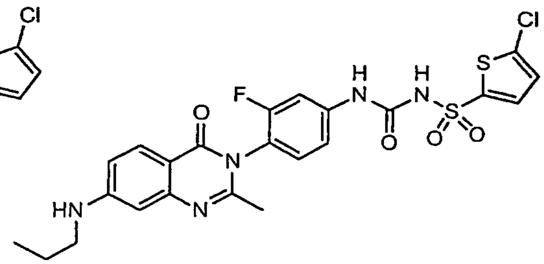
Example 695



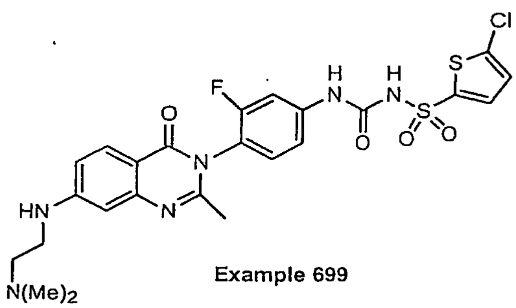
Example 696



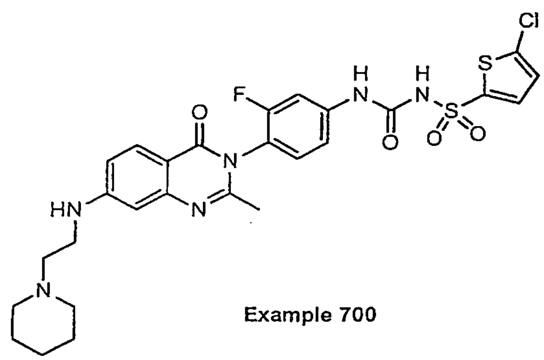
Example 697



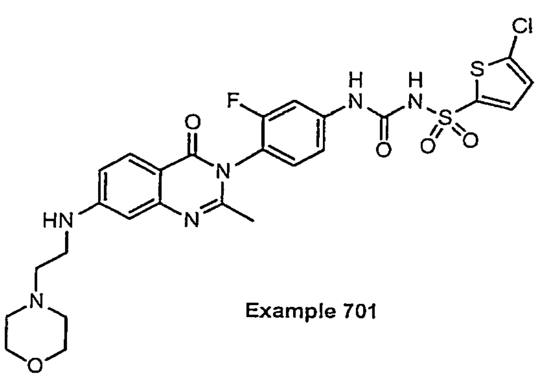
Example 698



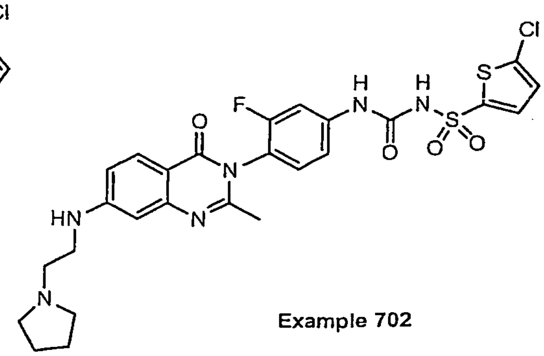
Example 699



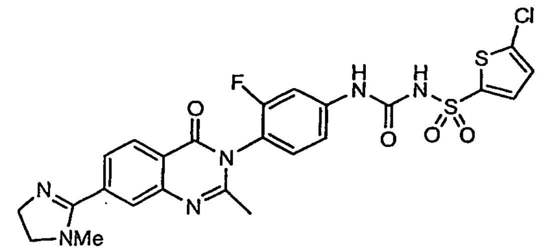
Example 700



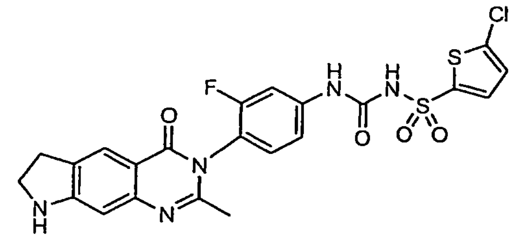
Example 701



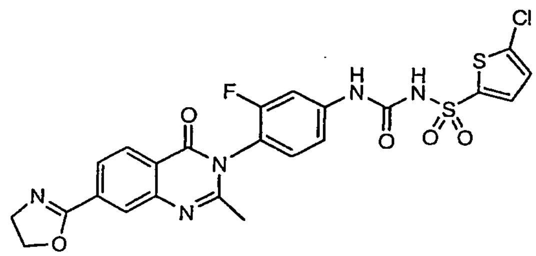
Example 702



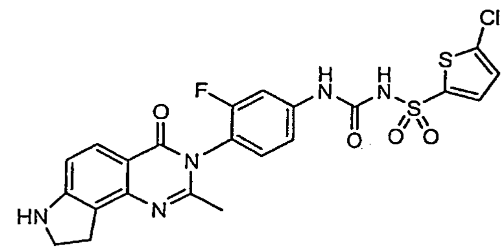
Example 703



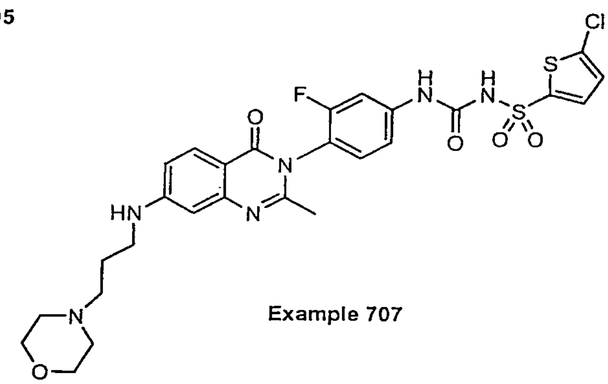
Example 704



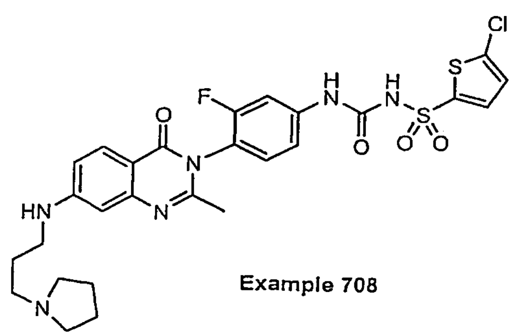
Example 705



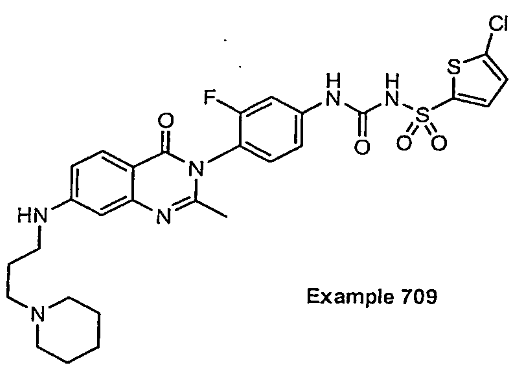
Example 706



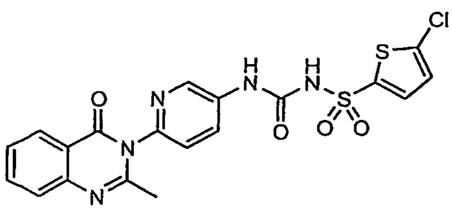
Example 707



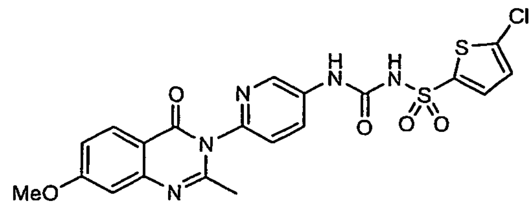
Example 708



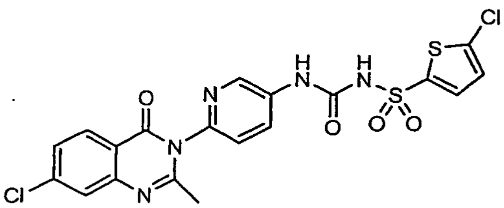
Example 709



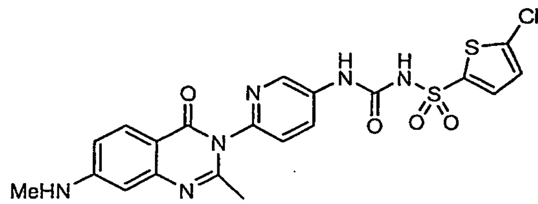
Example 710



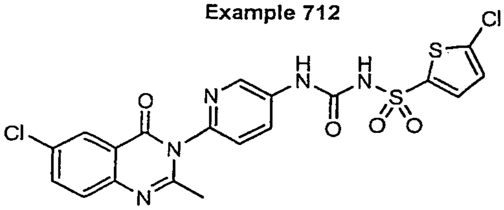
Example 711



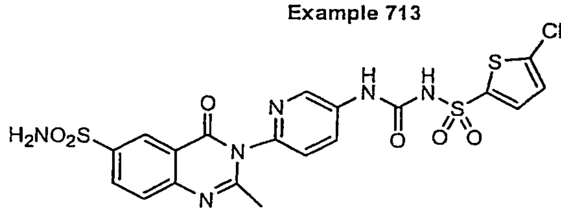
Example 712



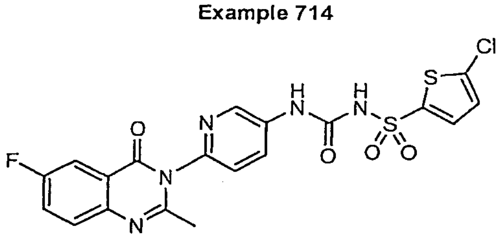
Example 713



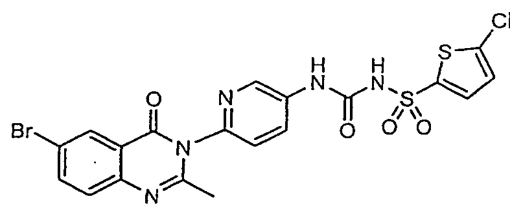
Example 714



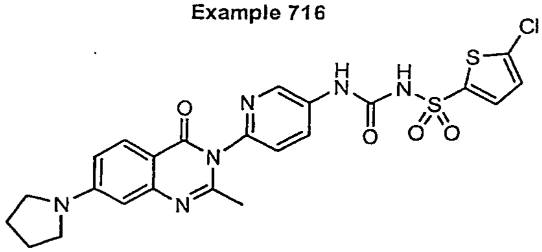
Example 715



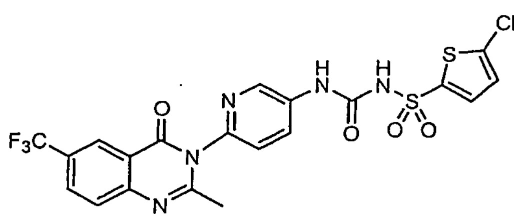
Example 716



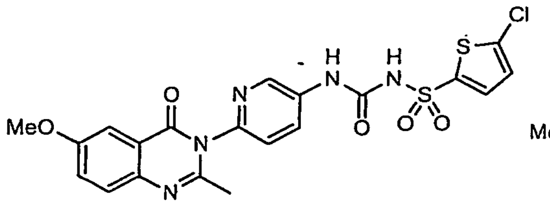
Example 717

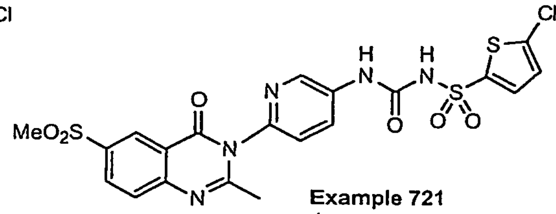


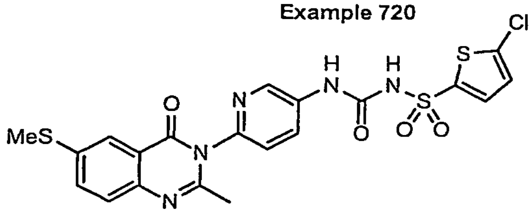
Example 718

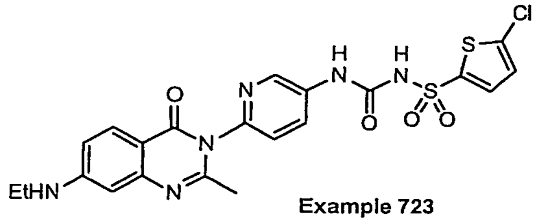


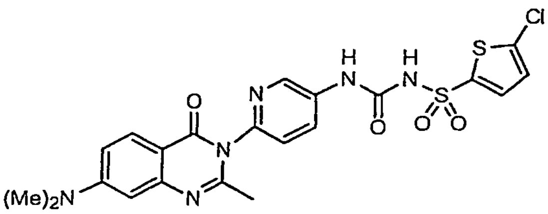
Example 719

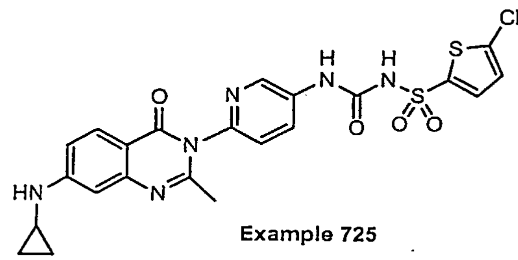

Example 720

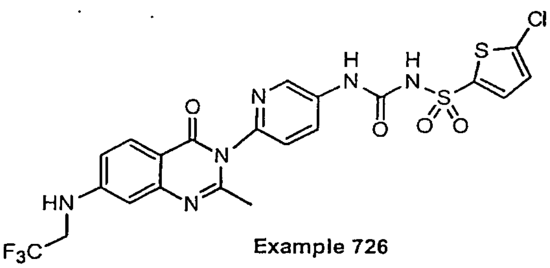

Example 721

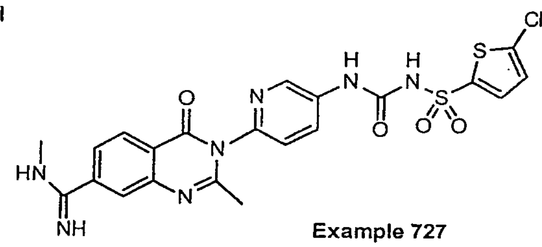

Example 722

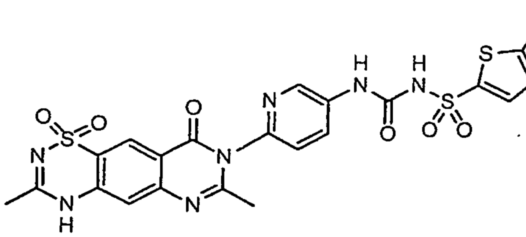

Example 723

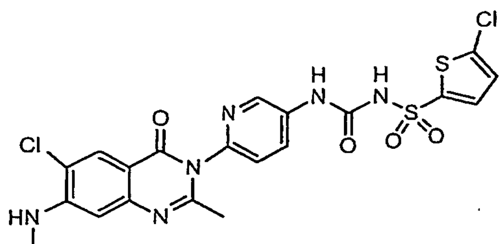

Example 724


Example 725

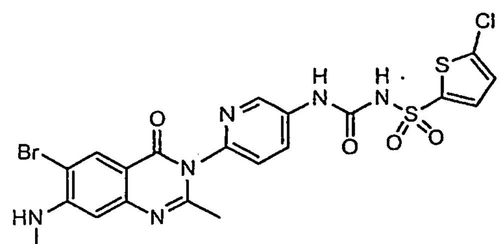

Example 726


Example 727

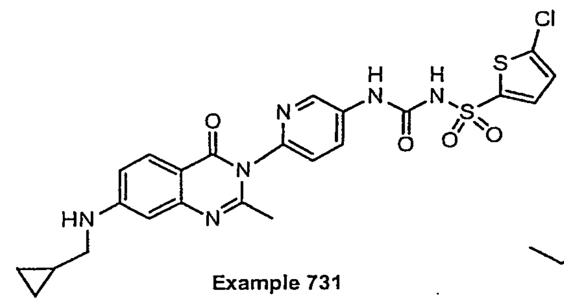

Example 728



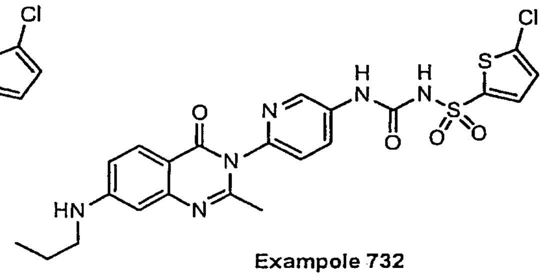
Example 729



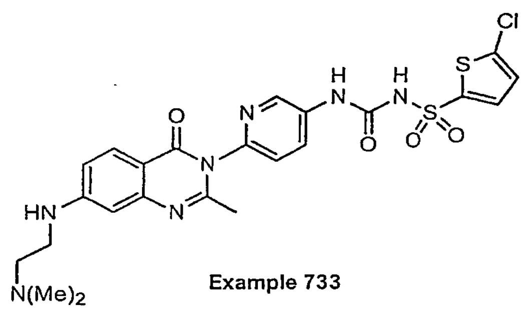
Example 730



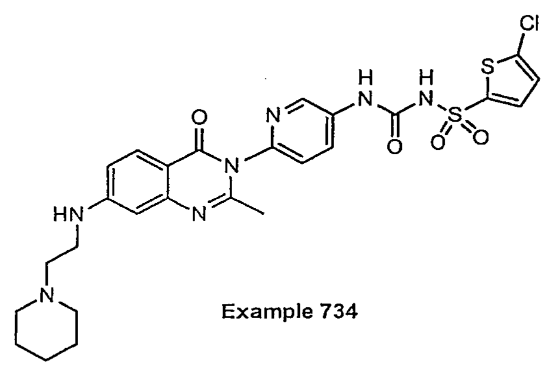
Example 731



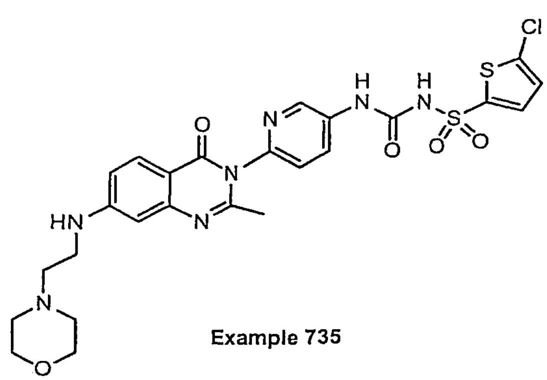
Exampole 732



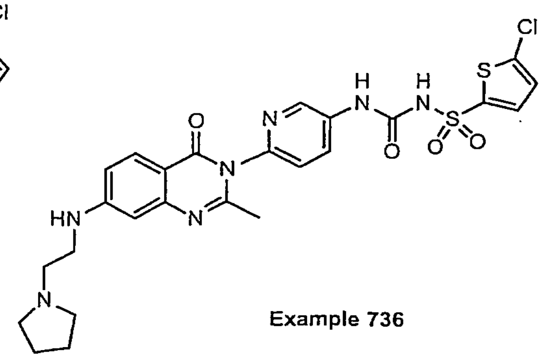
Example 733



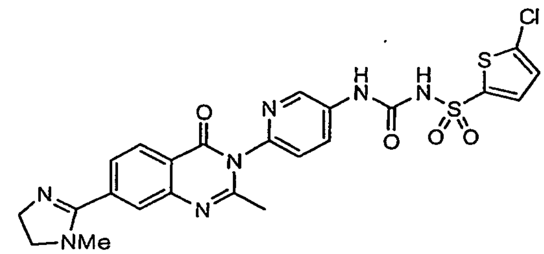
Example 734



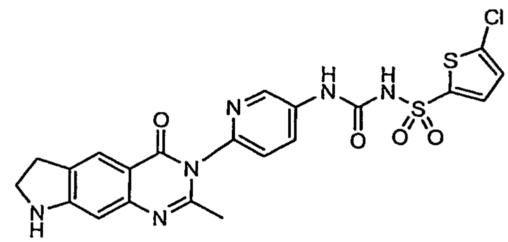
Example 735



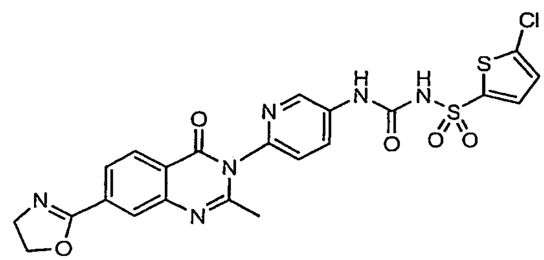
Example 736



Example 737



Example 738



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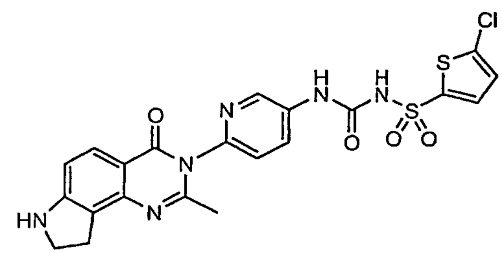
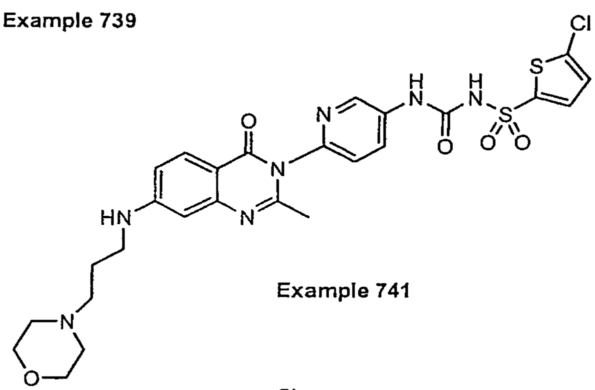


Example 740



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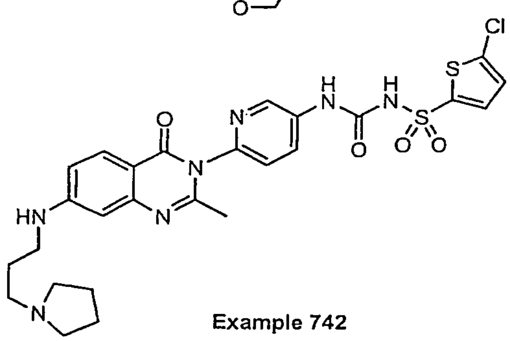
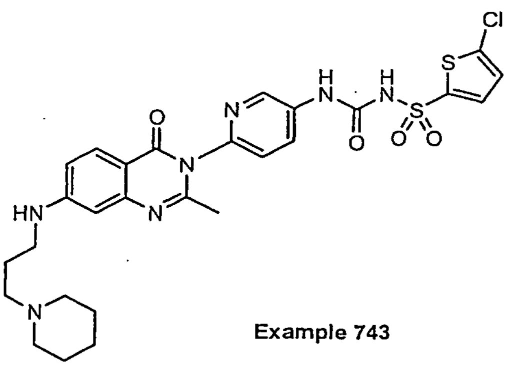


Example 742



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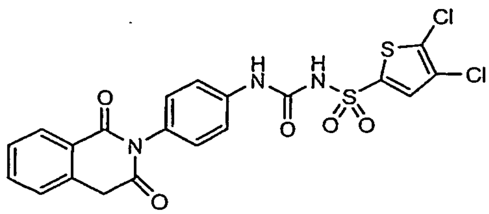

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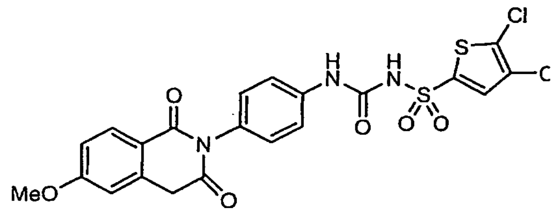

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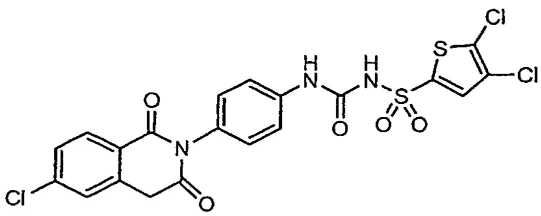
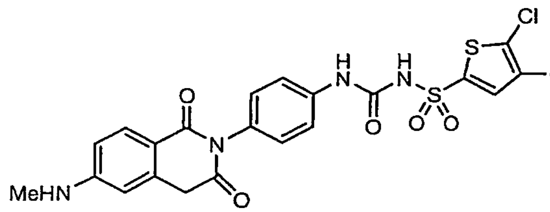
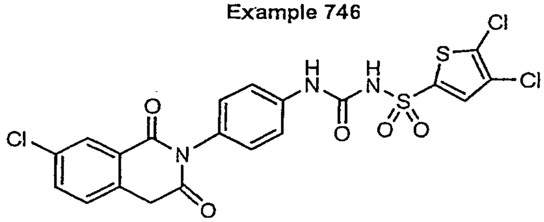


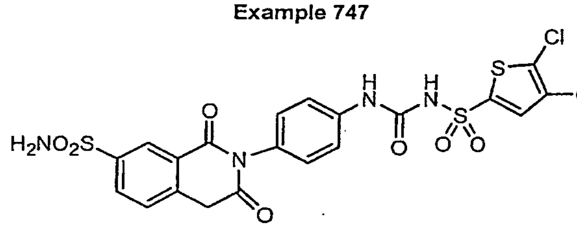
Example 746



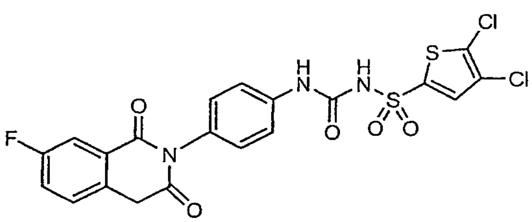
Example 747



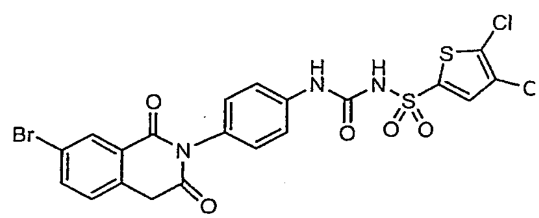
Example 748



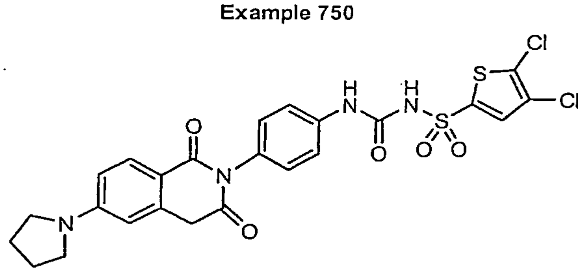
Example 749



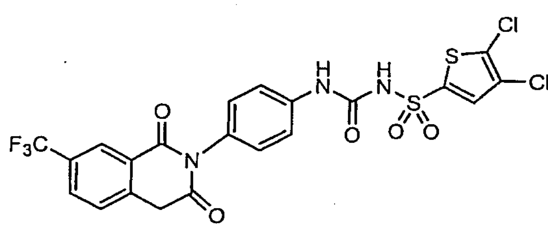
Example 750



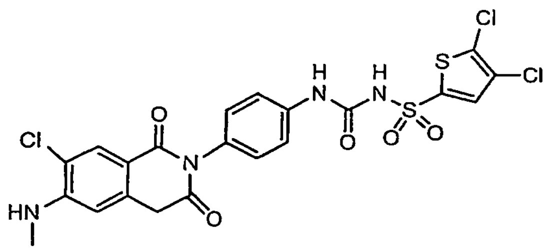
Example 751



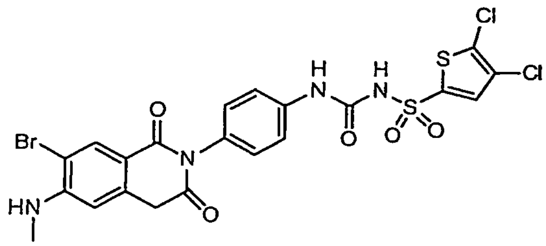
Example 752



Example 753



Example 754



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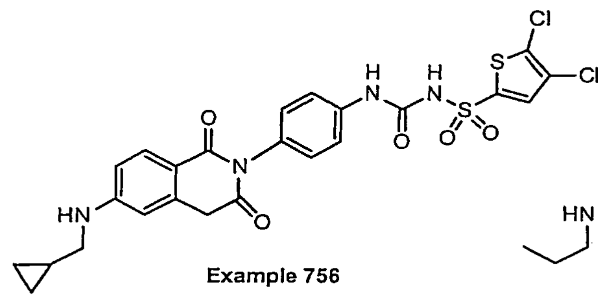
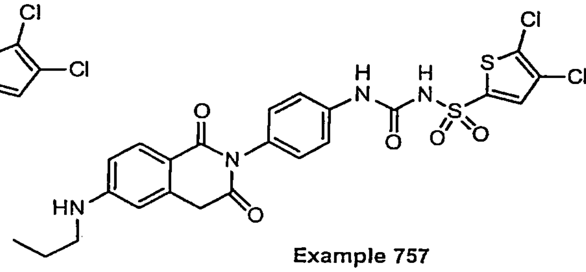
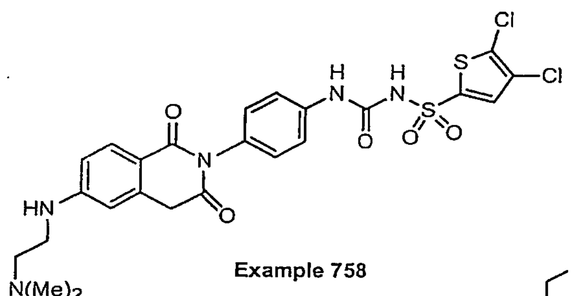


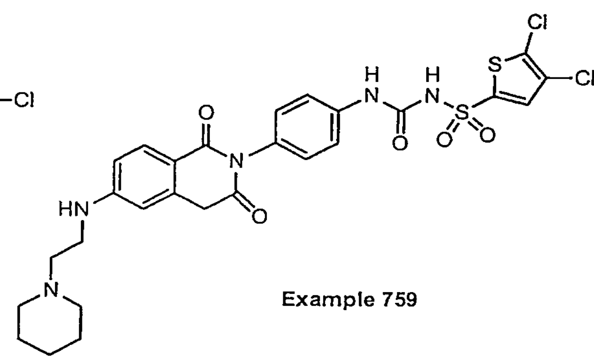
Example 756



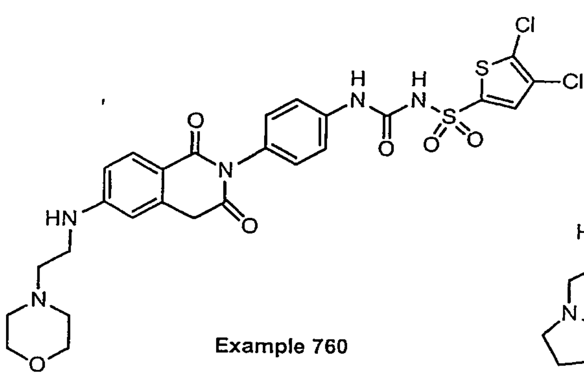
Example 757



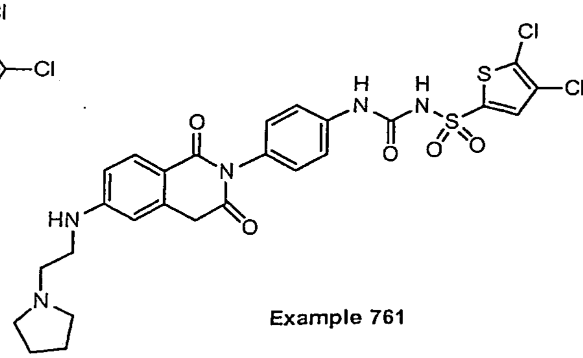
Example 758



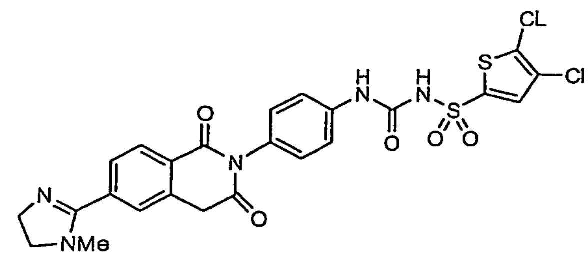
Example 759



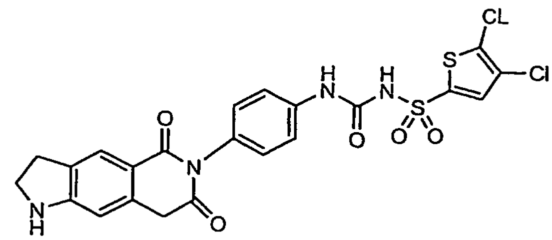
Example 760



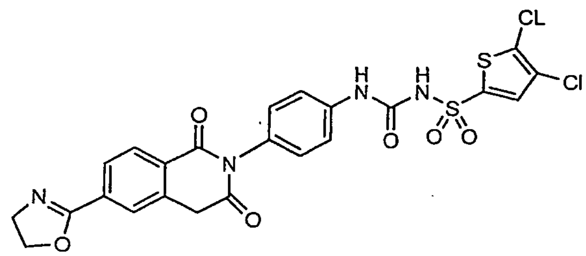
Example 761



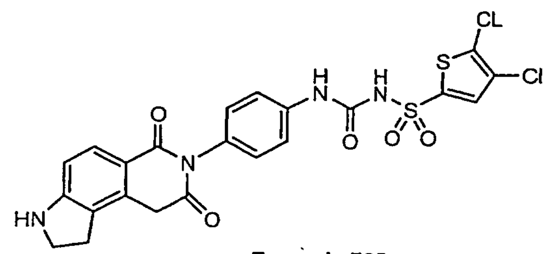
Example 762



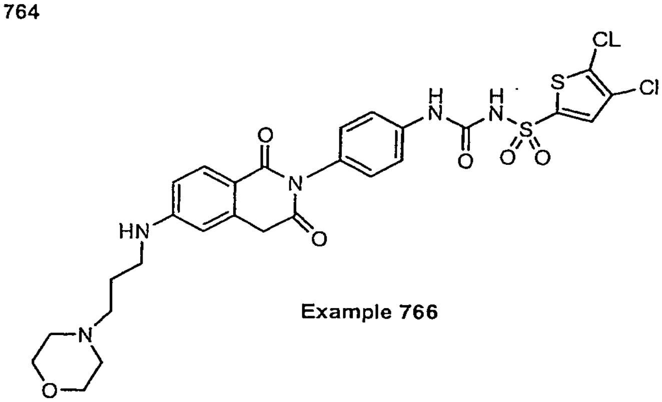
Example 763



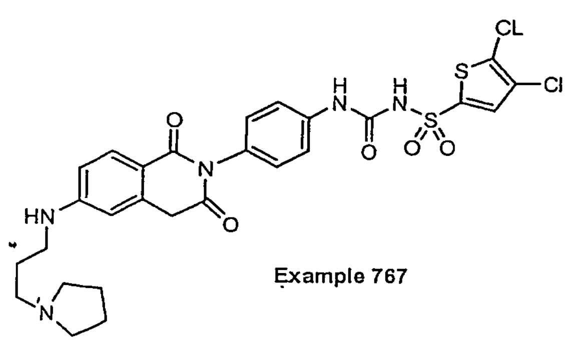
Example 764



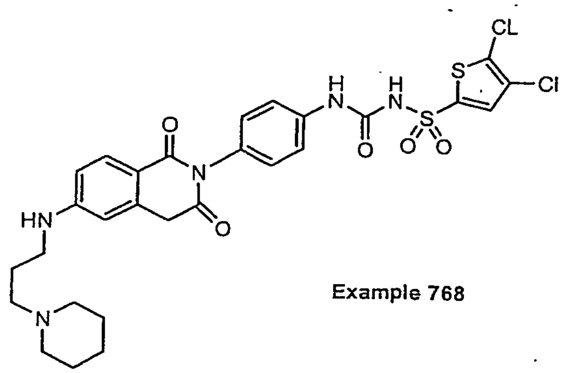
Example 765



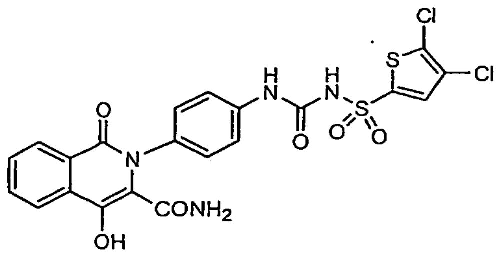
Example 766



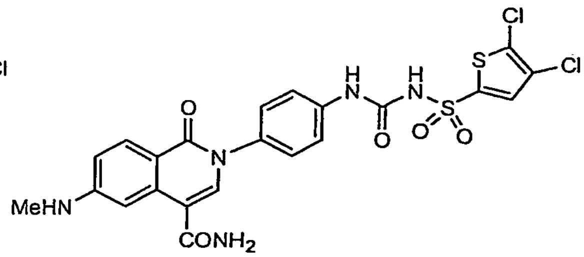
Example 767



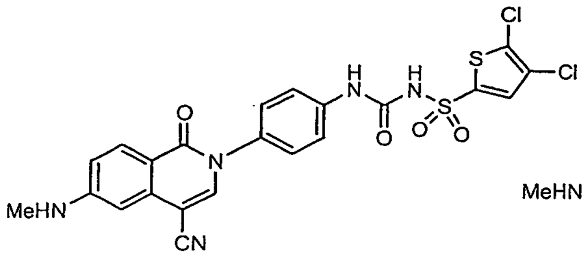
Example 768



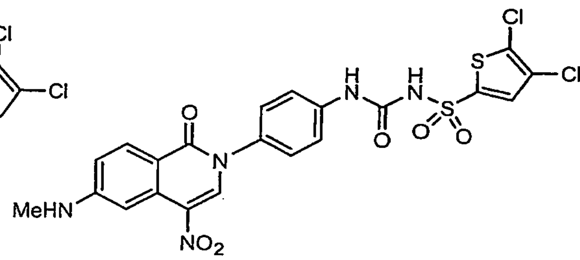
Example 769



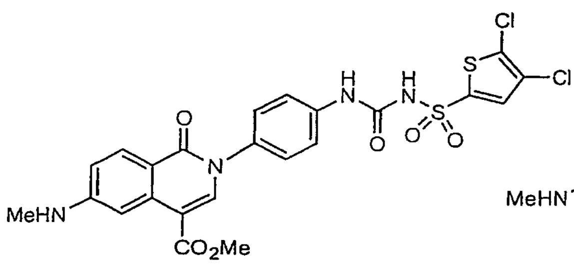
Example 770



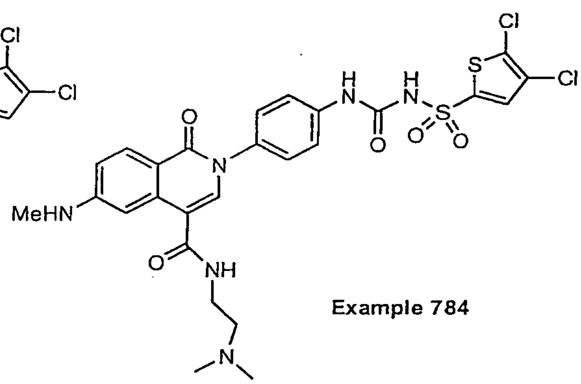
Example 781



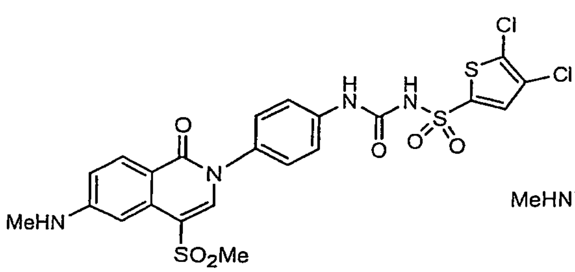
Example 782



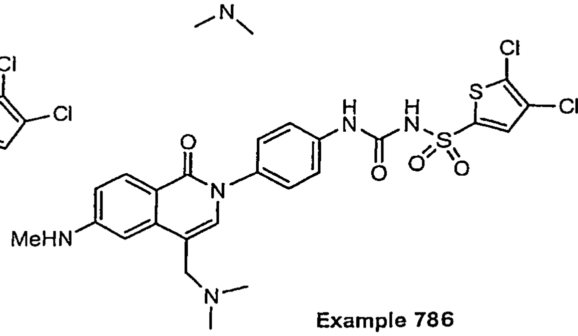
Example 783



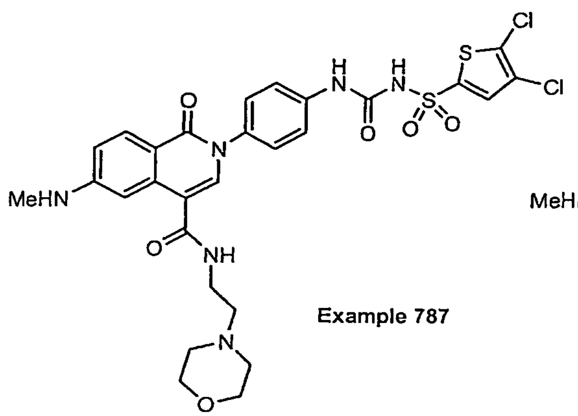
Example 784



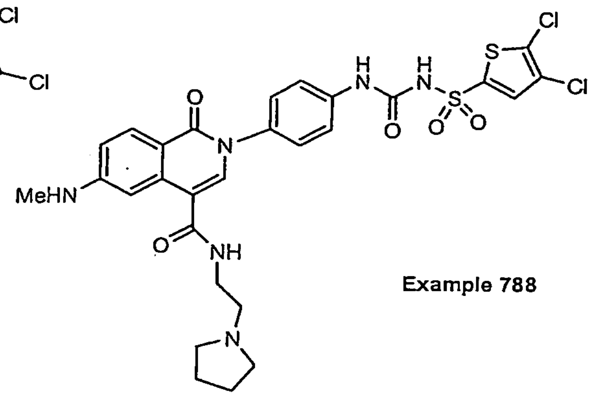
Example 785



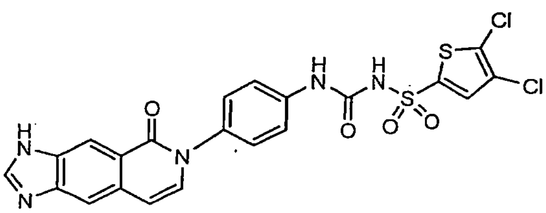
Example 786



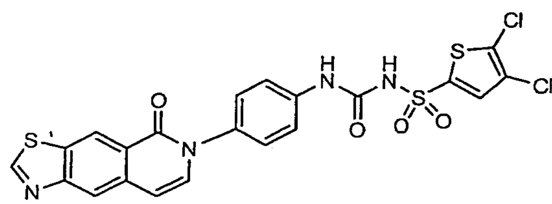
Example 787



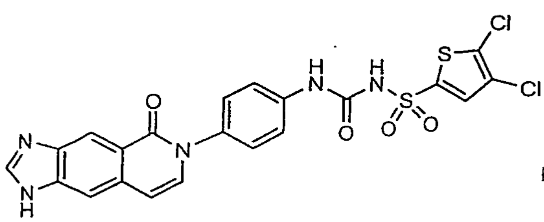
Example 788



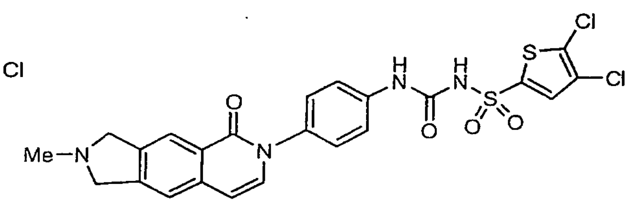
Example 789



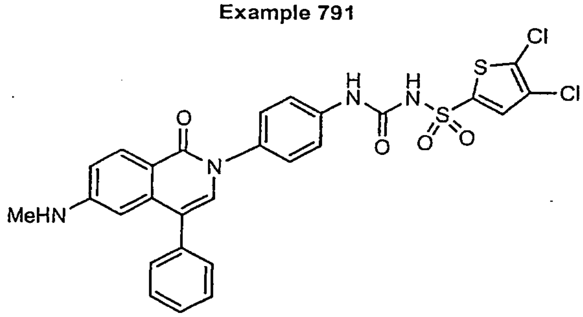
Examp;le 790



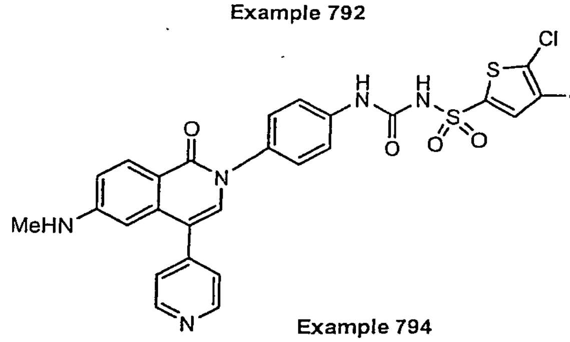
Example 791



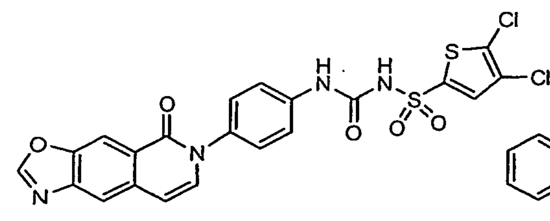
Example 792



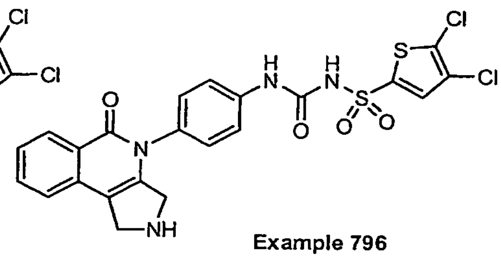
Example 793



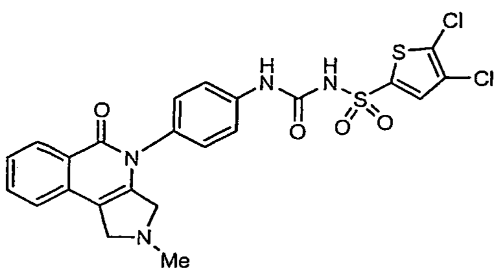
Example 794



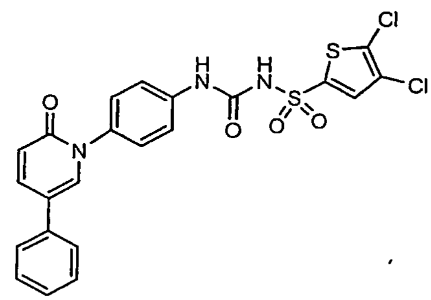
Example 795



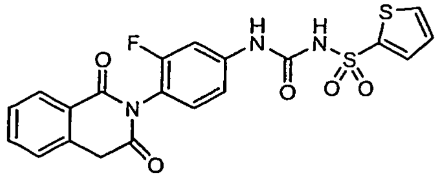
Example 796



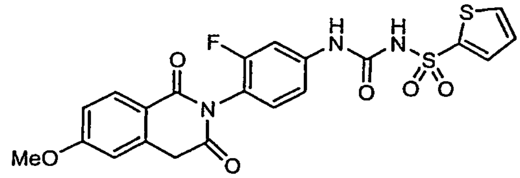
Example 797



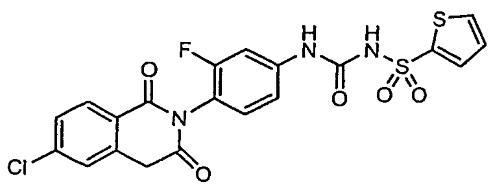
Example 798



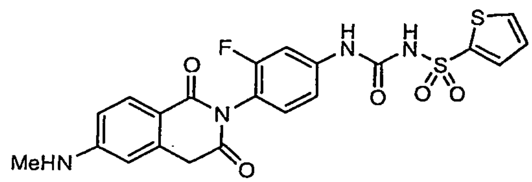
Example 799



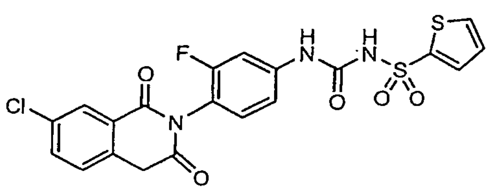
Example 800



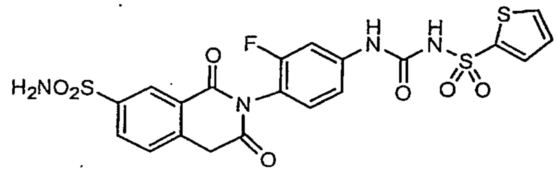
Example 801



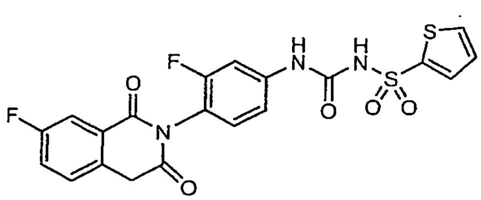
Example 802



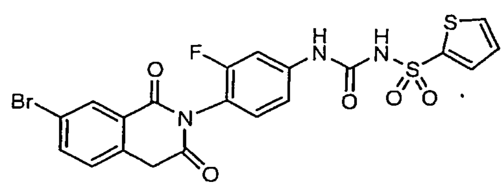
Example 803



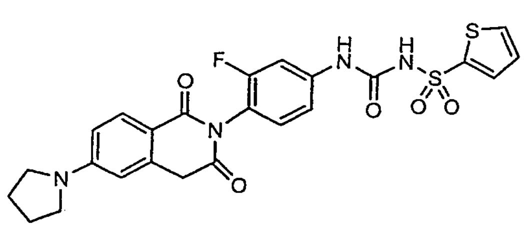
Example 804



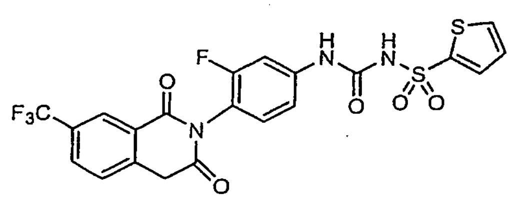
Example 805



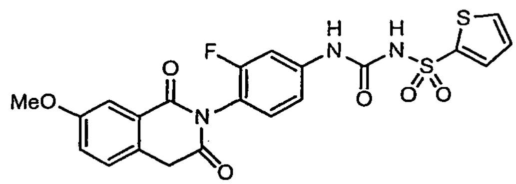
Example 806



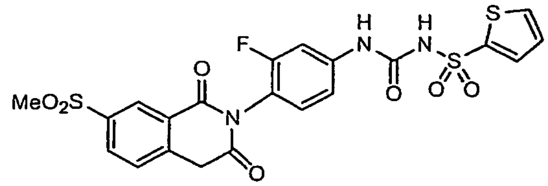
Example 807



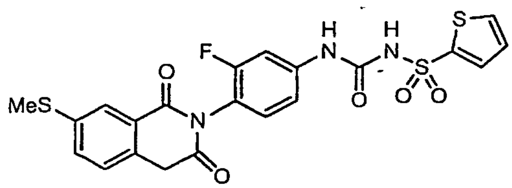
Example 808



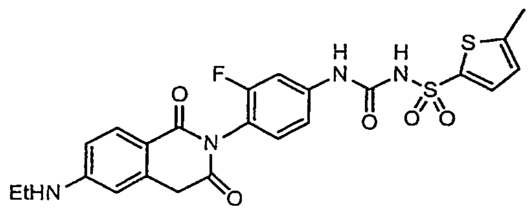
Example 809



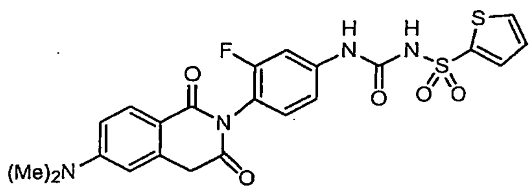
Example 810



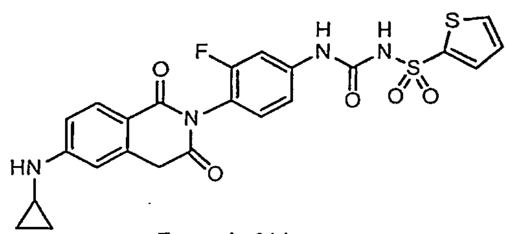
Example 811



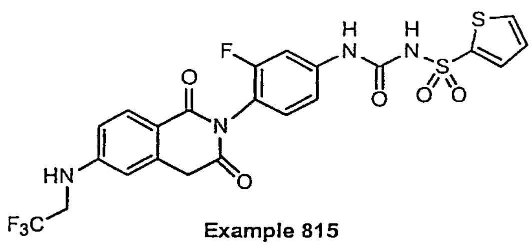
Example 812



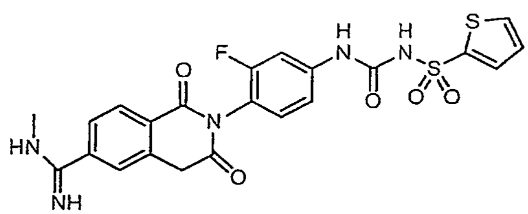
Example 813



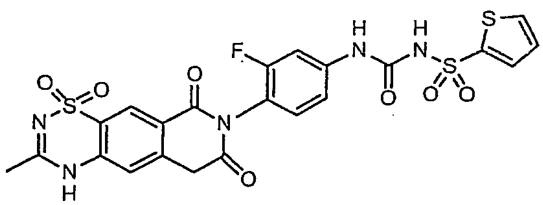
Example 814



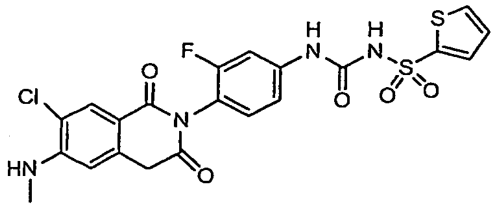
Example 815



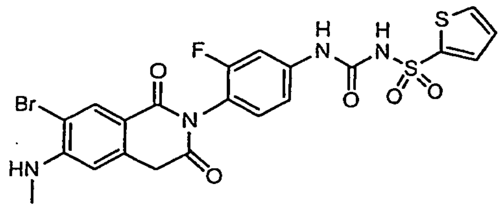
Example 816



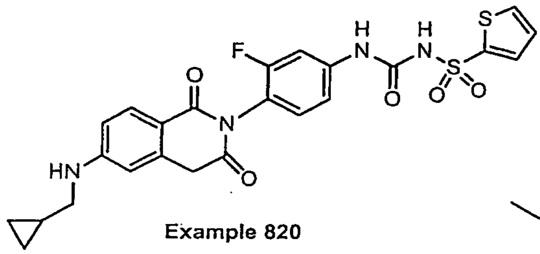
Example 817



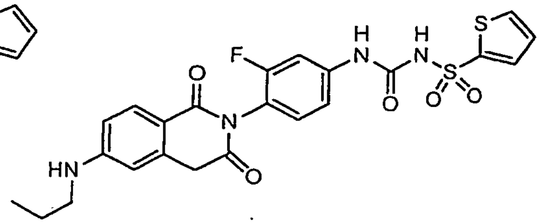
Example 818



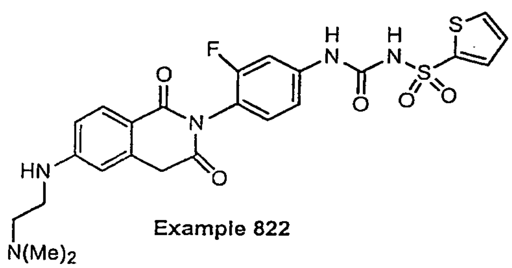
Example 819



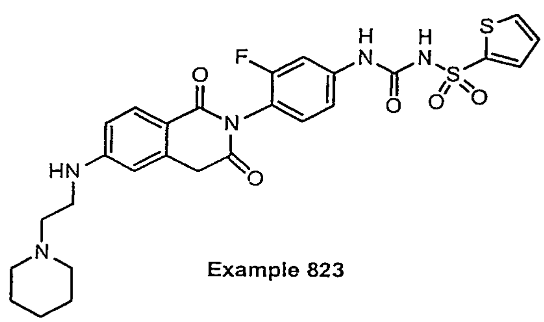
Example 820



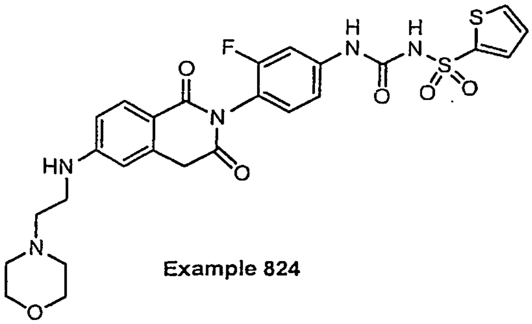
Example 821



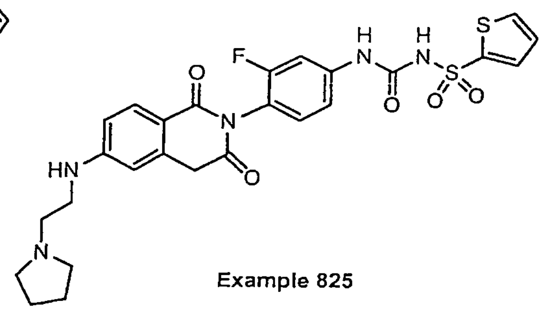
Example 822



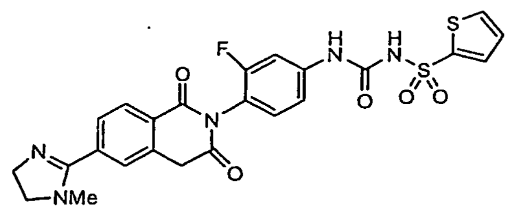
Example 823



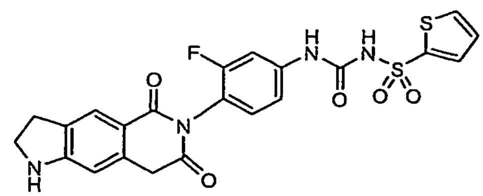
Example 824



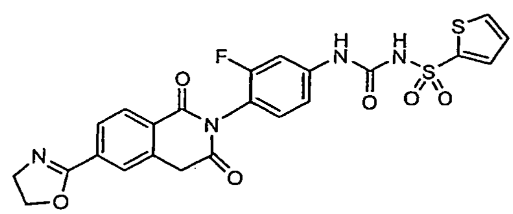
Example 825



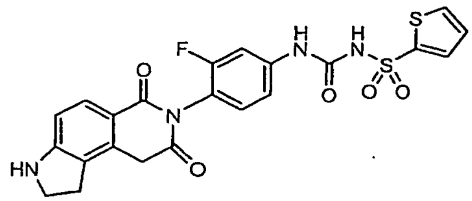
Example 826



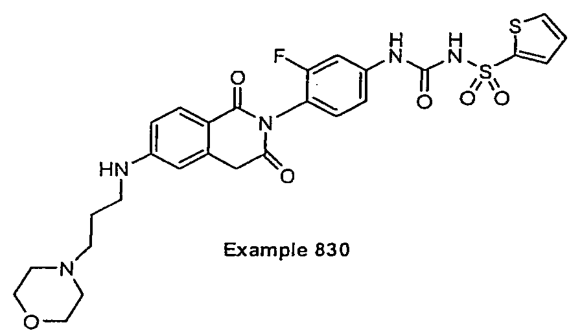
Example 827



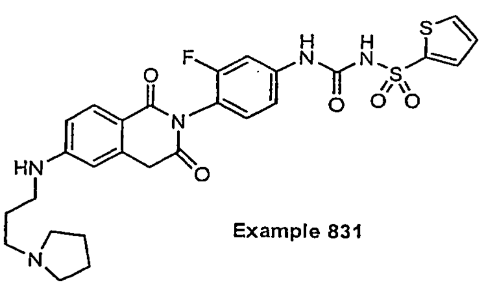
Example 828



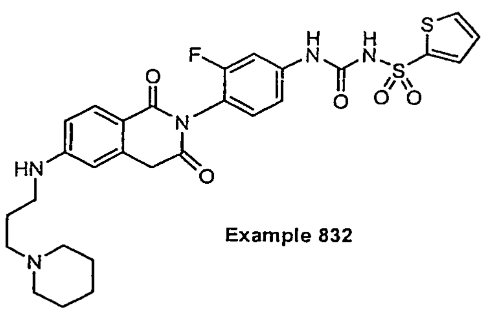
Example 829



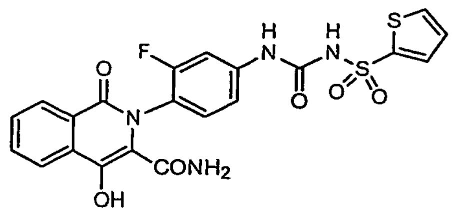
Example 830



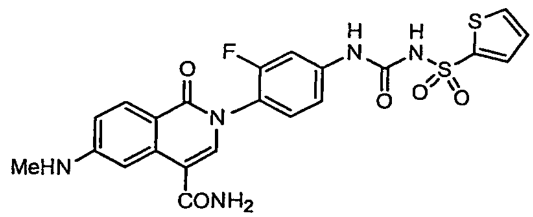
Example 831



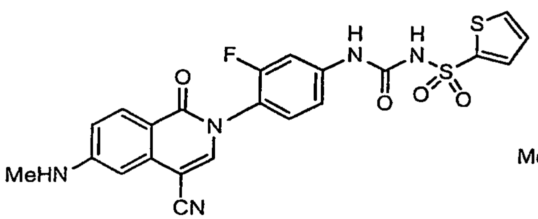
Example 832



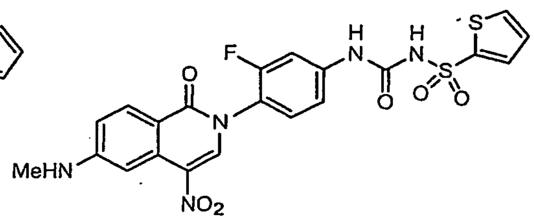
Example 833



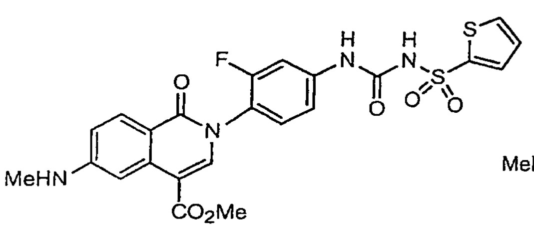
Example 834



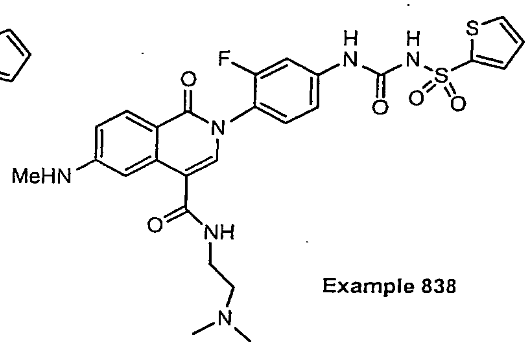
Example 835



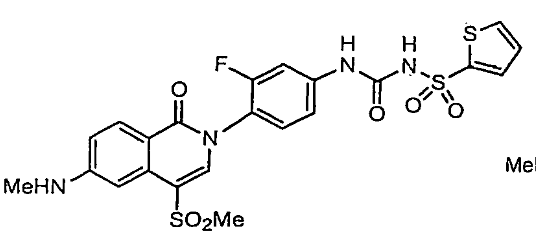
Example 836



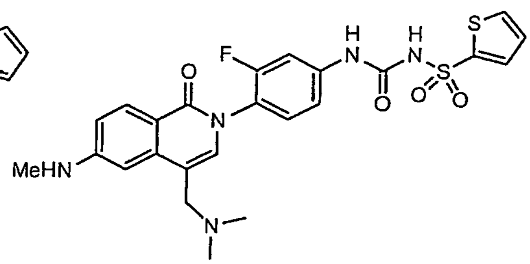
Example 837



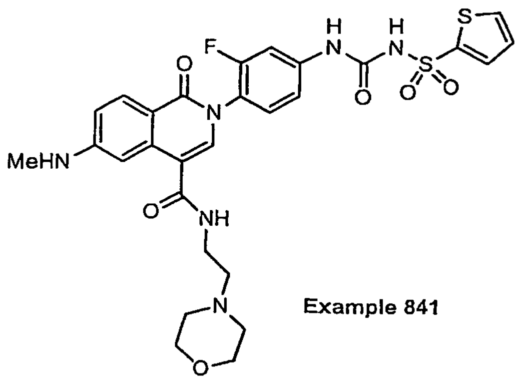
Example 838



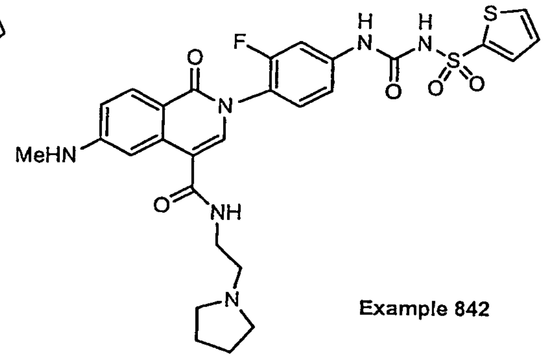
Example 839



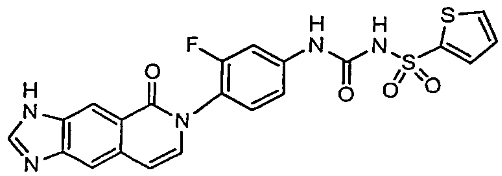
Example 840



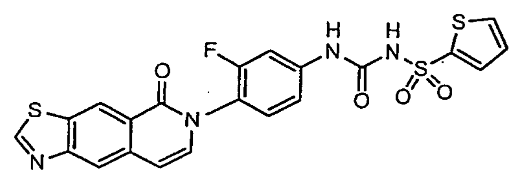
Example 841



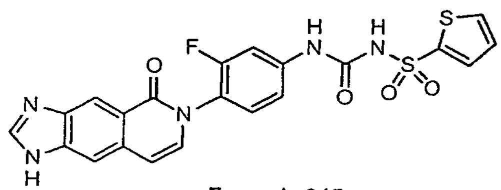
Example 842



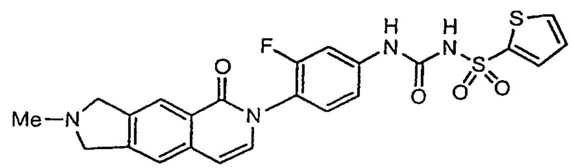
Example 843



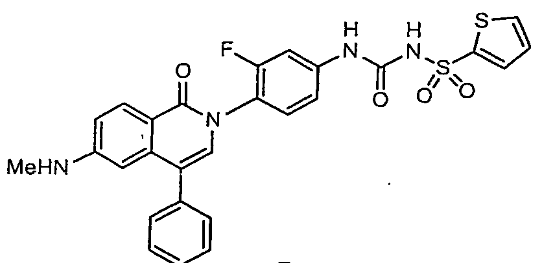
Example 844



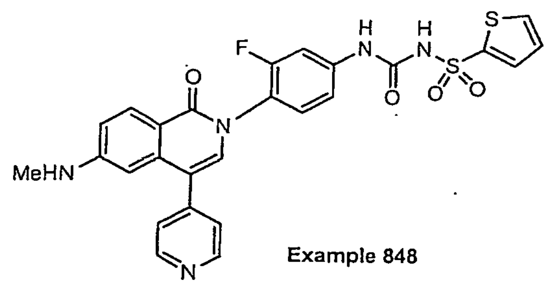
Example 845



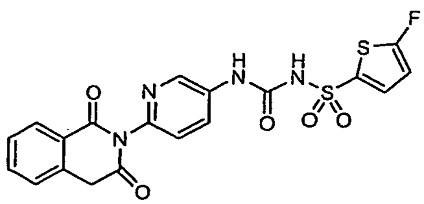
Example 846



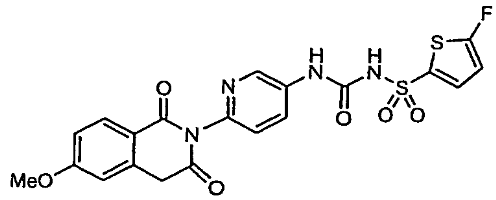
Example 847



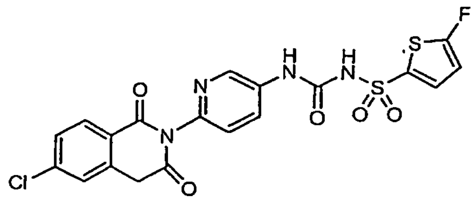
Example 848



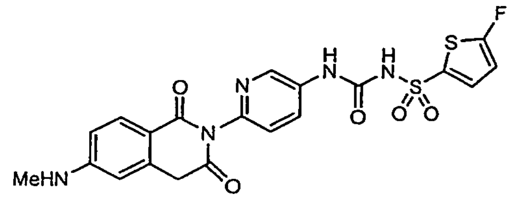
Example 849



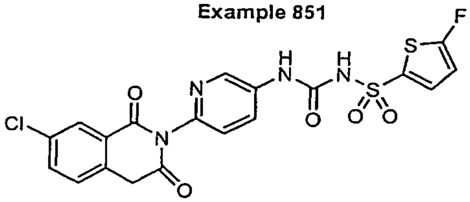
Example 850



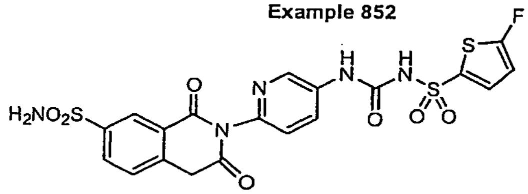
Example 851



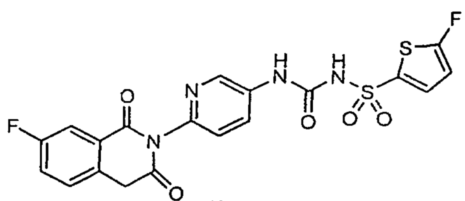
Example 852



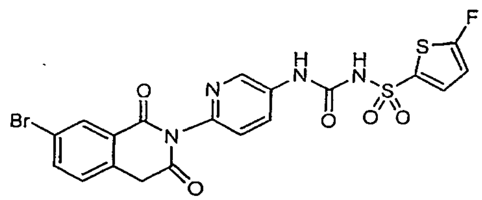
Example 853



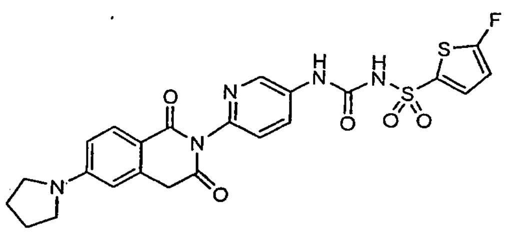
example 854



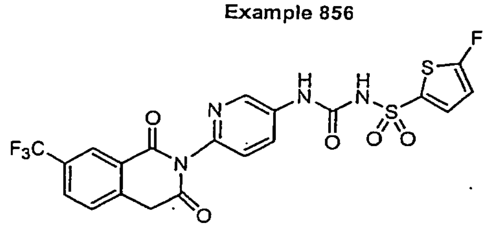
Example 855



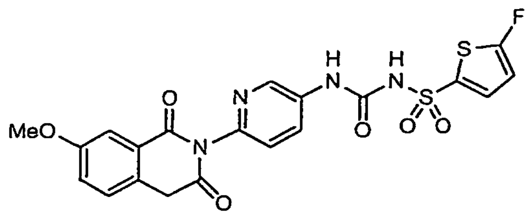
Example 856



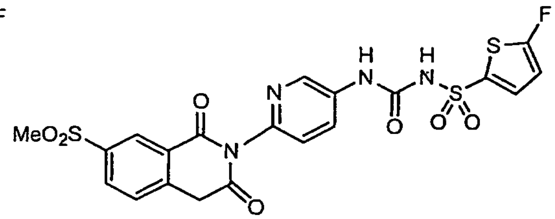
Example 857



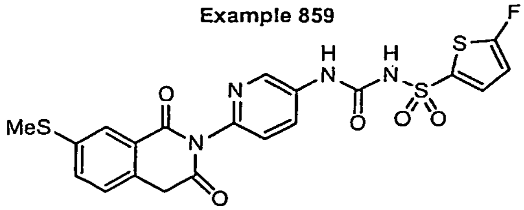
Example 858



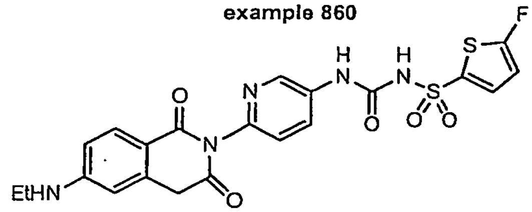
Example 859



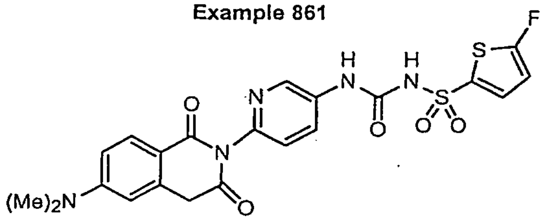
example 860



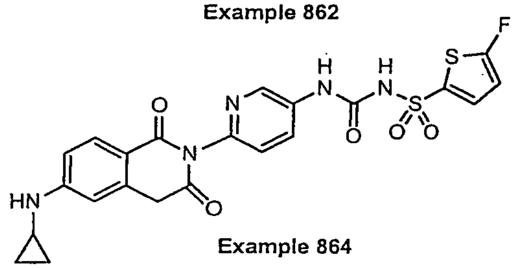
Example 861



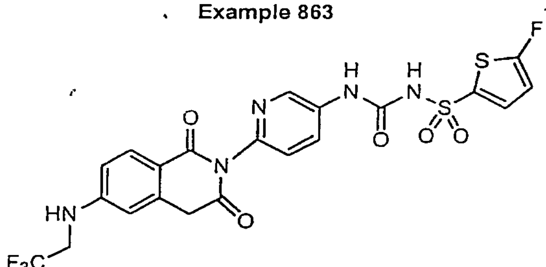
Example 862



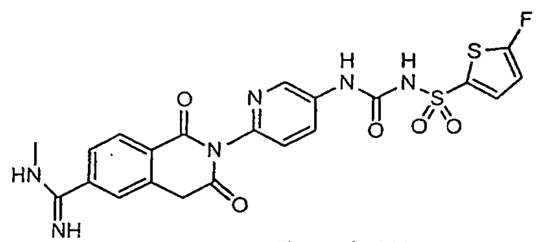
Example 863



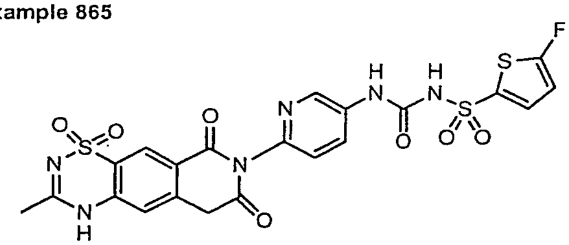
Example 864



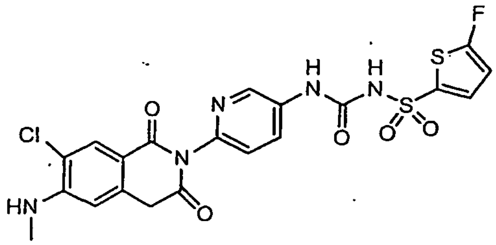
Example 865



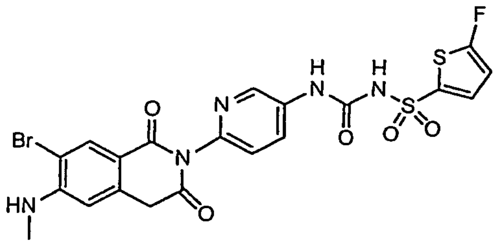
Example 866



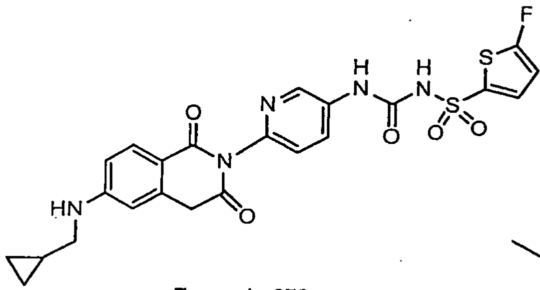
Example 867



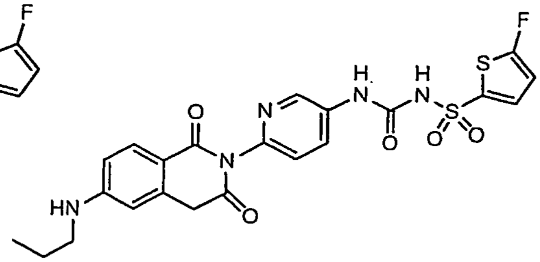
Example 868



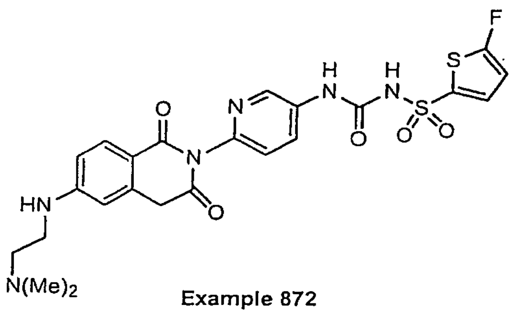
Example 869



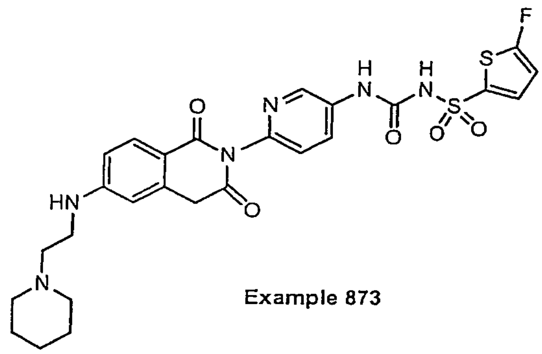
Example 870



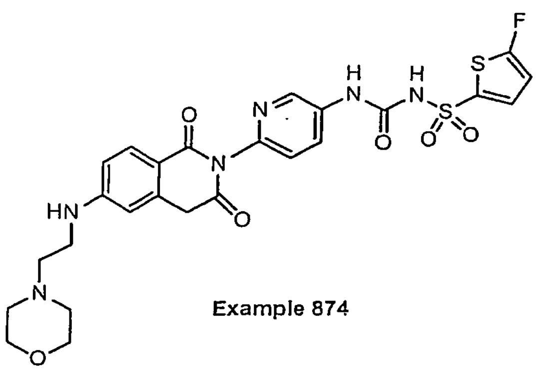
Example 871



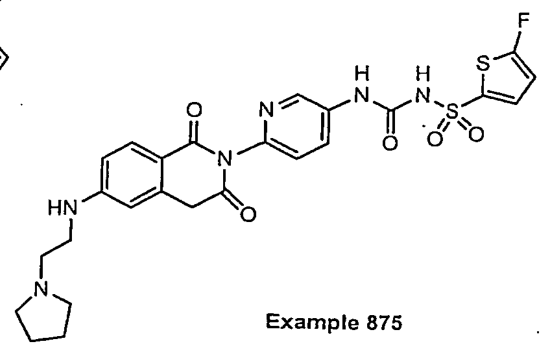
Example 872



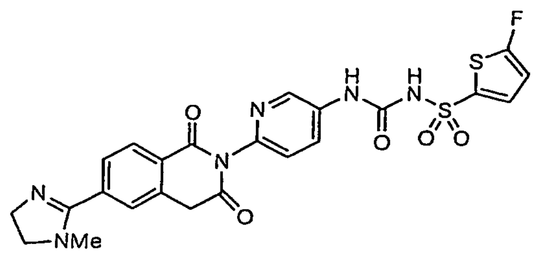
Example 873



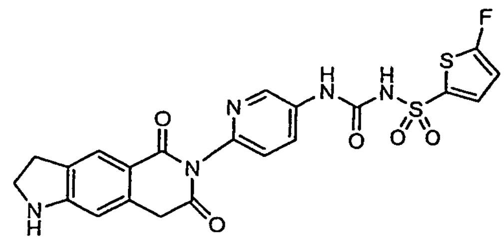
Example 874



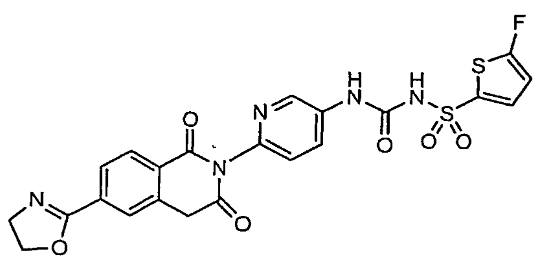
Example 875



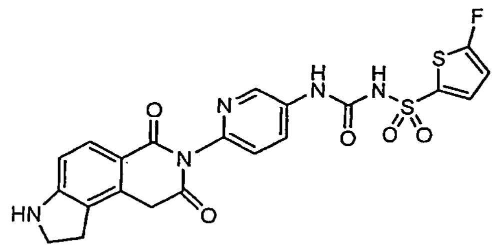
Example 876



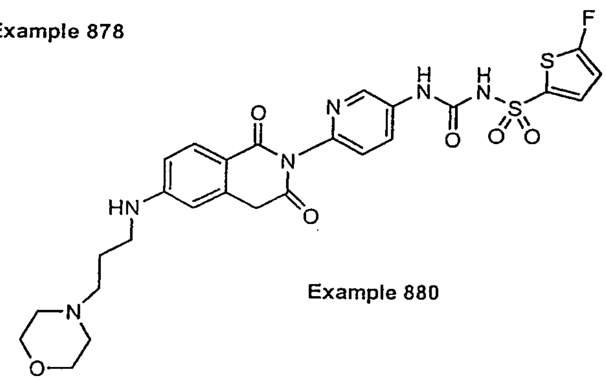
Example 877



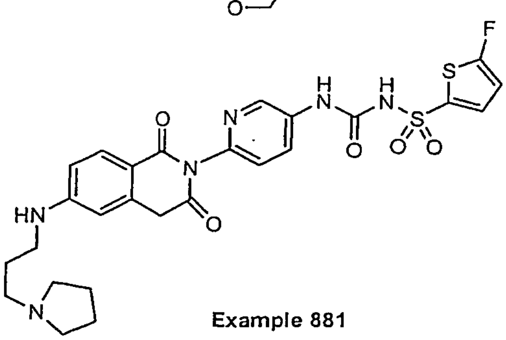
Example 878



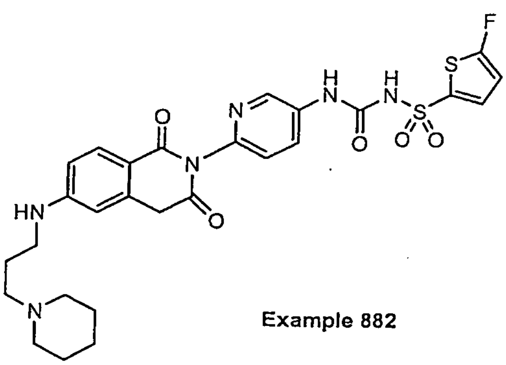
Example 879



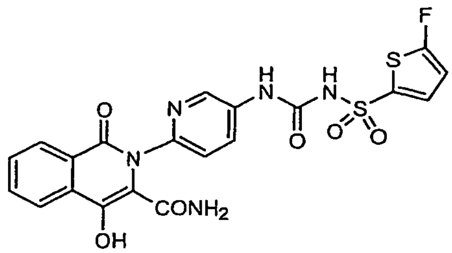
Example 880



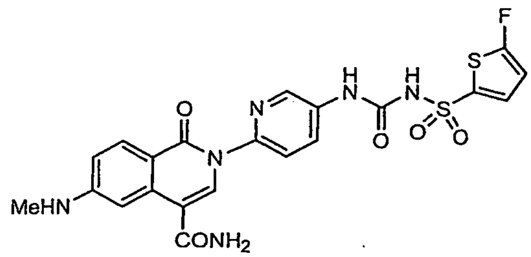
Example 881



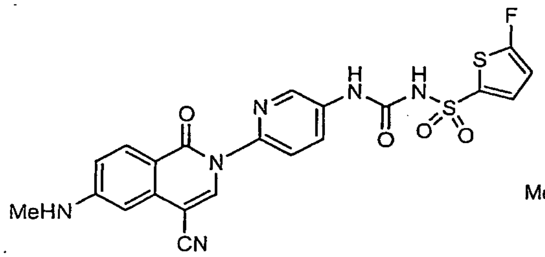
Example 882



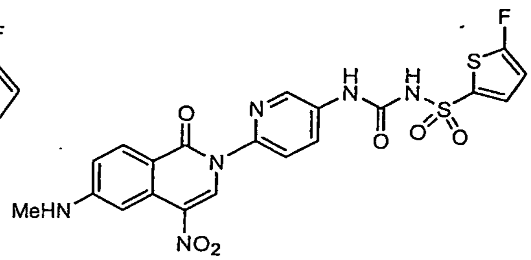
Example 883



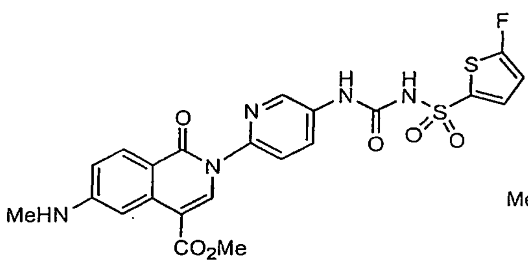
Example 884



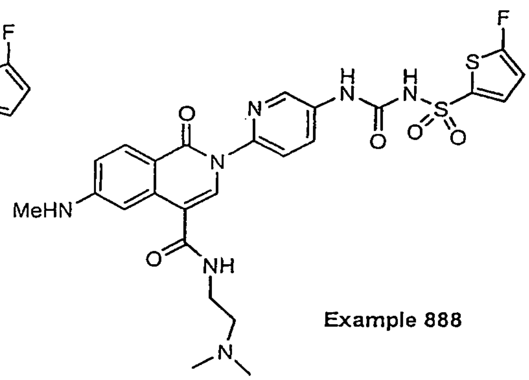
Example 885



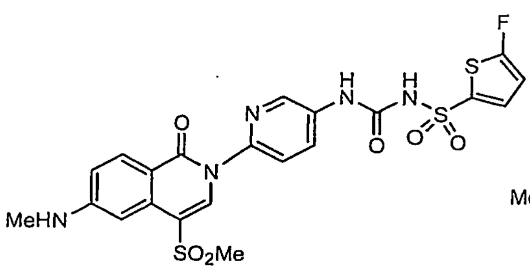
Example 886



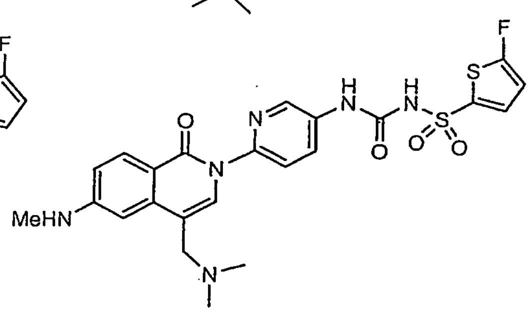
Example 887



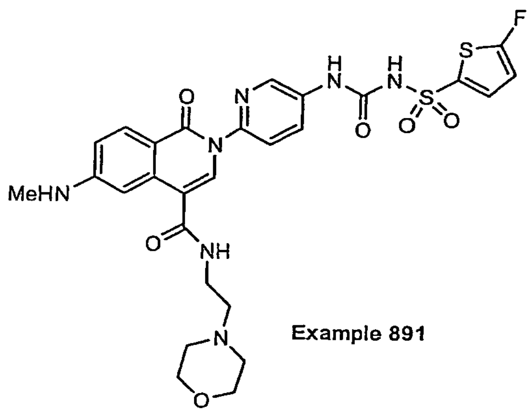
Example 888



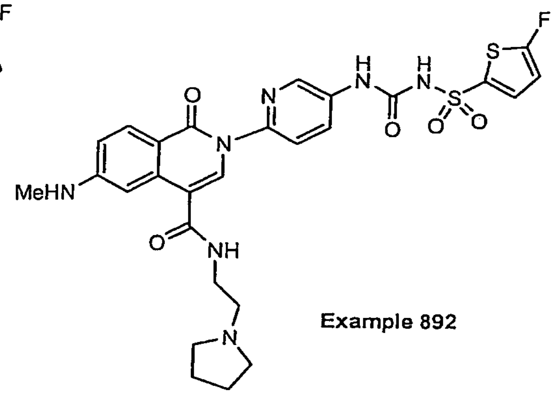
Example 889



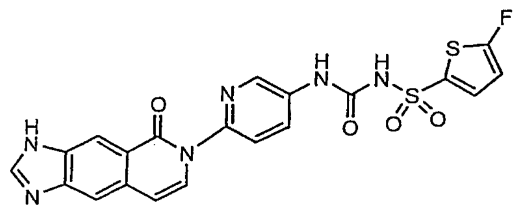
Example 890



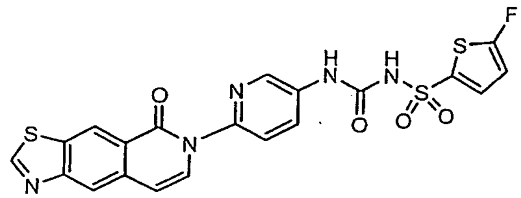
Example 891



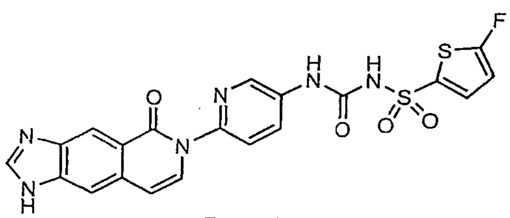
Example 892



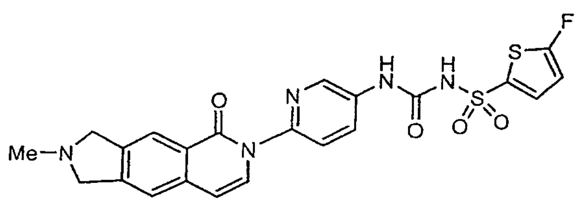
Example 893



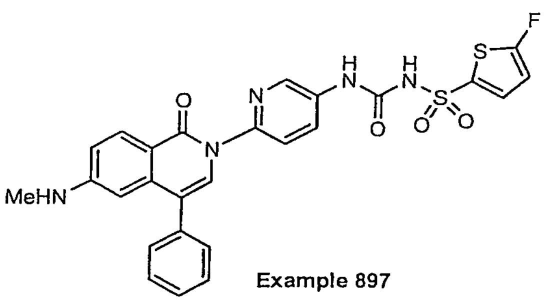
Example 894



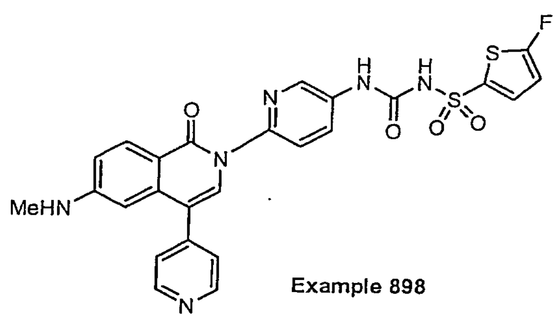
Example 895



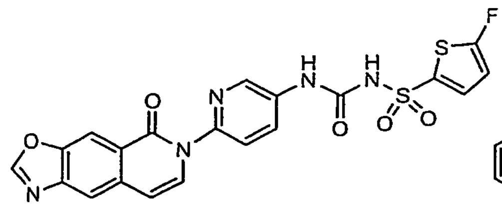
Example 896



Example 897



Example 898



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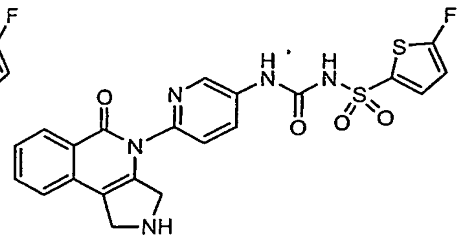
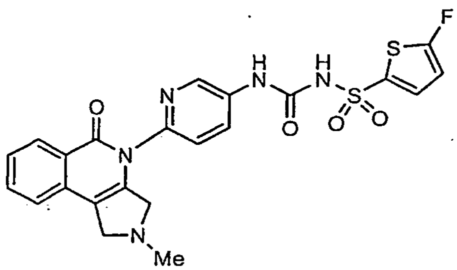
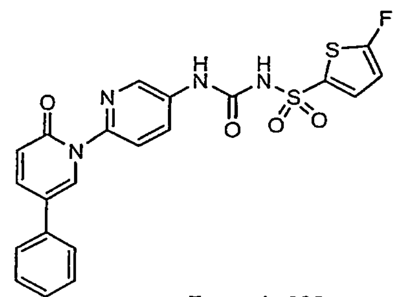


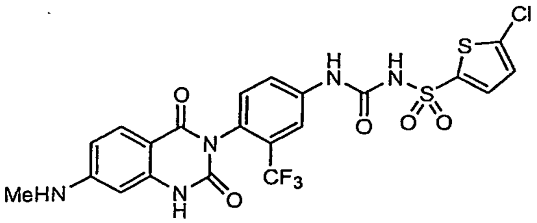
Example 900



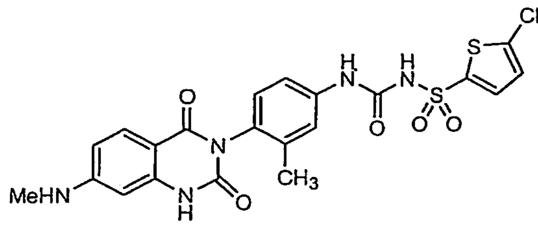
Example 901



Example 902



Example 903



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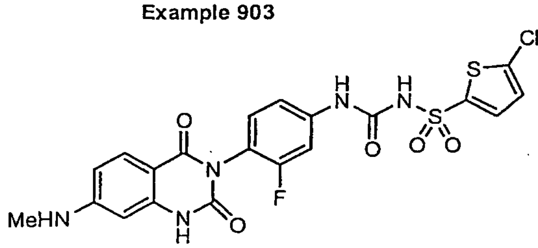

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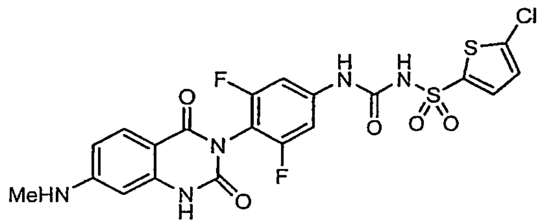
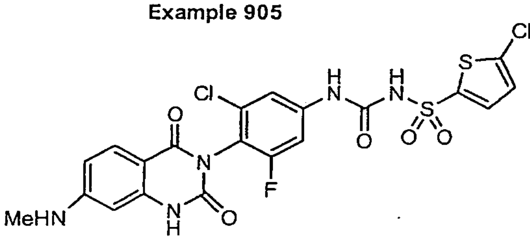


Example 906



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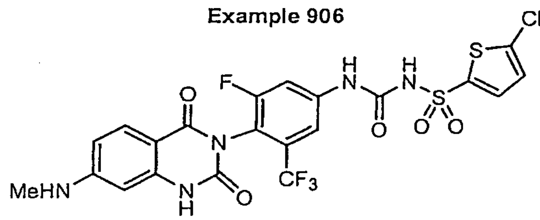
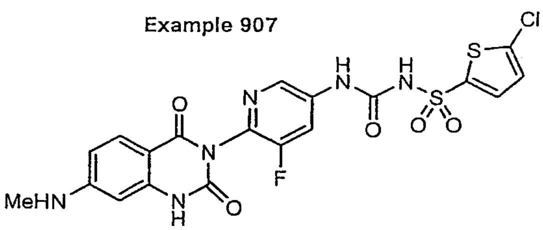


Example 908



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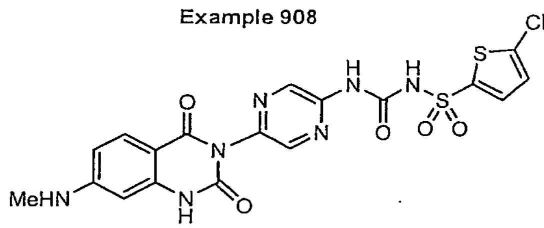
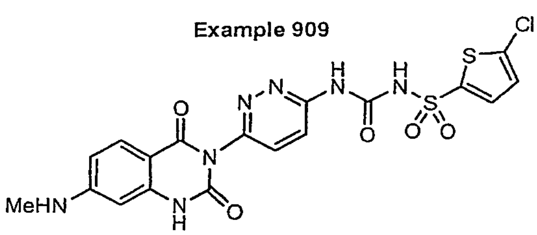
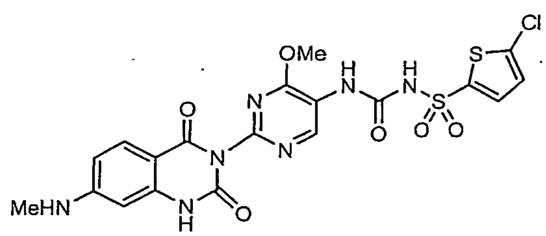


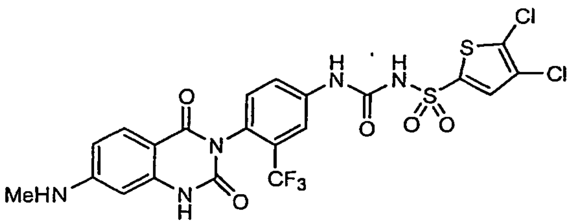
Example 910



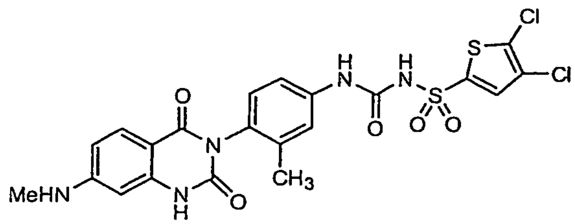
Example 911



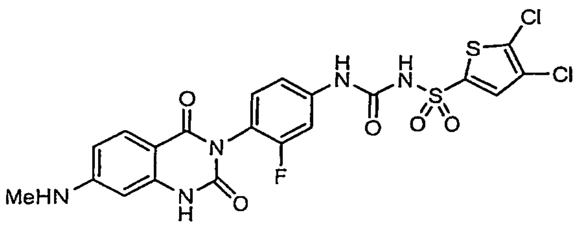
Example 912



Example 913



Example 914



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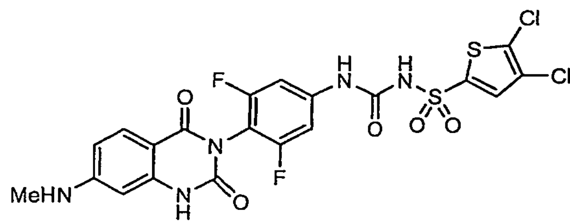
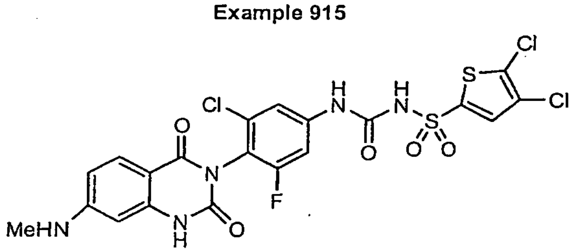
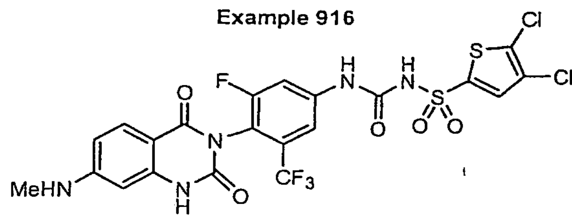


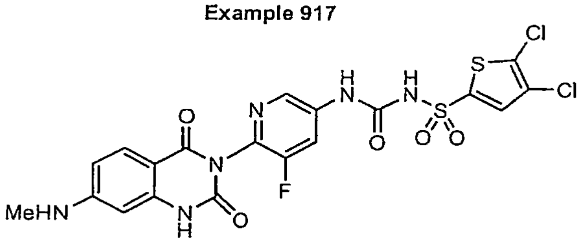
Example 916



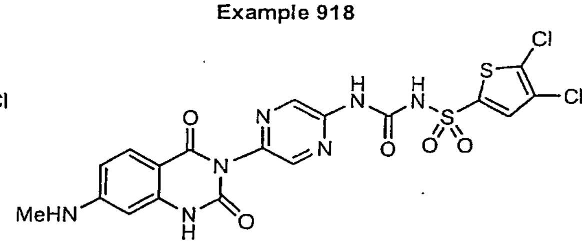
Example 917



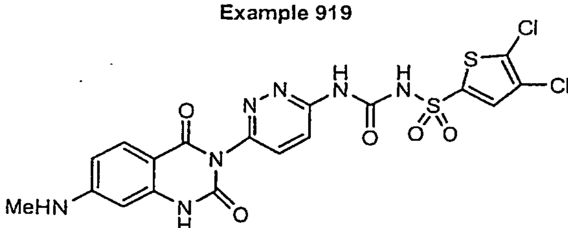
Example 918



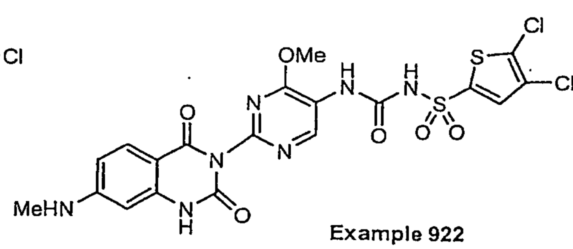
Example 919



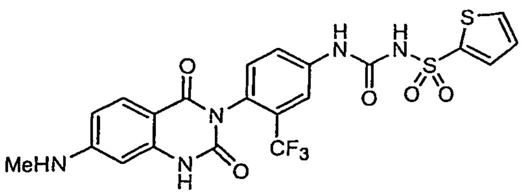
Example 920



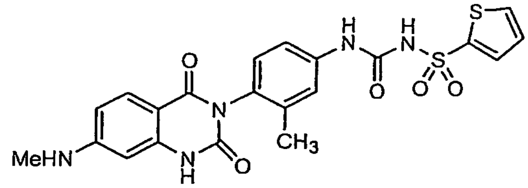
Example 921



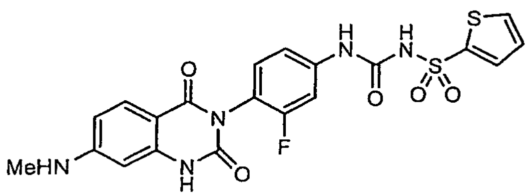
Example 922



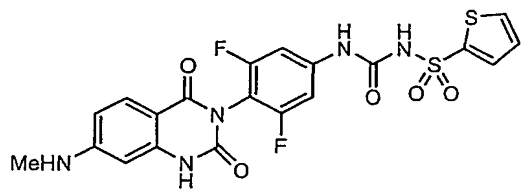
Example 923



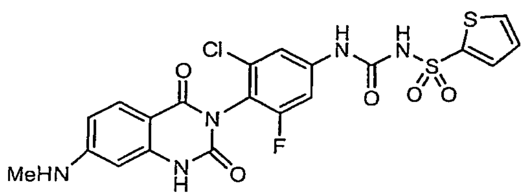
Example 924



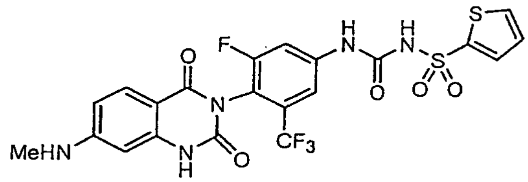
Example 925



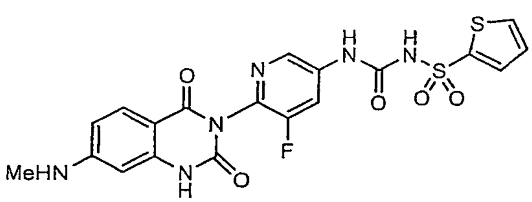
Example 926



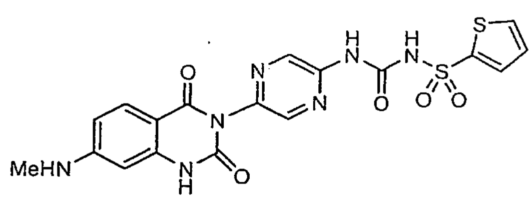
Example 927



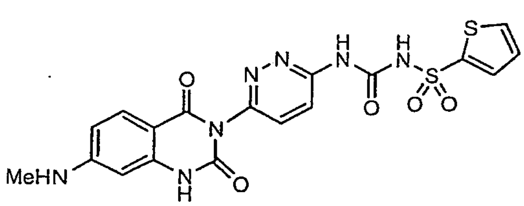
Example 928



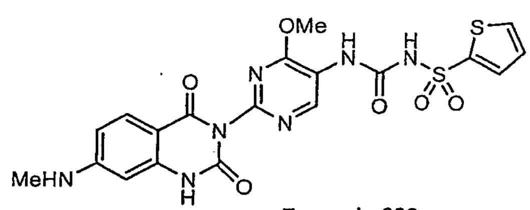
Example 929



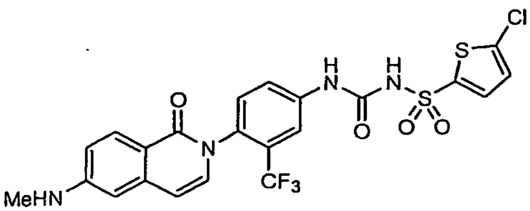
Example 930



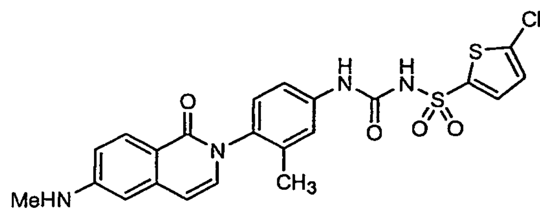
Example 931



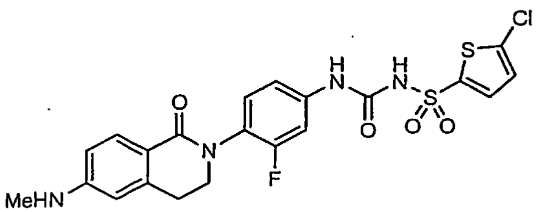
Example 932



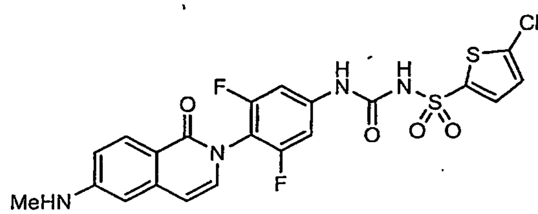
Example 933



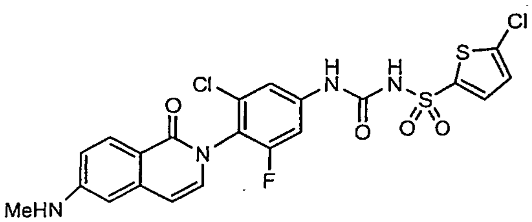
Example 934



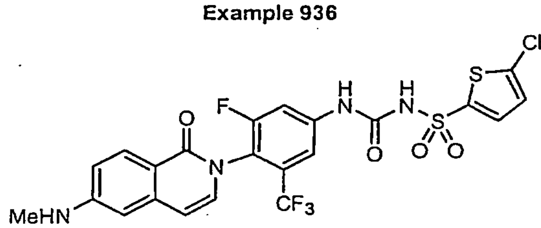
Example 935



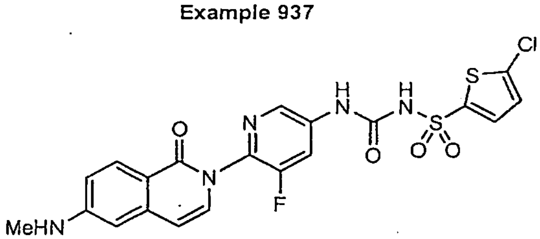
Example 936



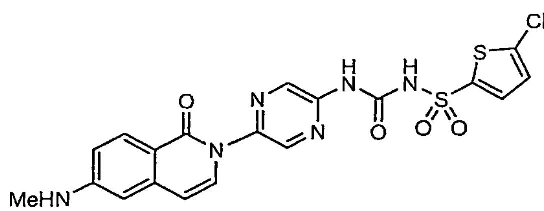
Example 937



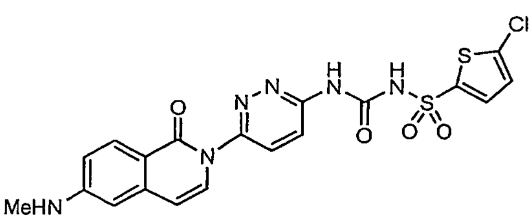
Example 938



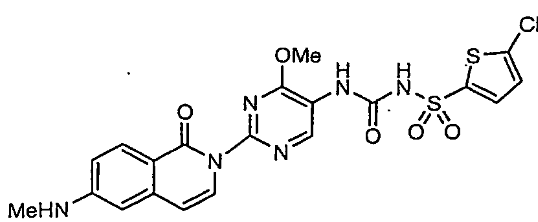
Example 939



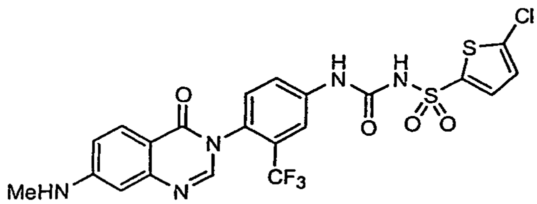
Example 940



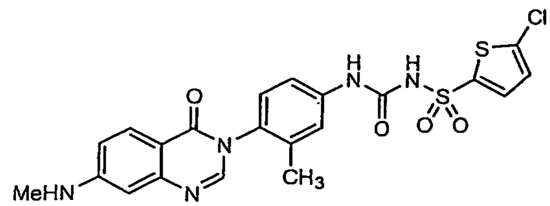
Example 941



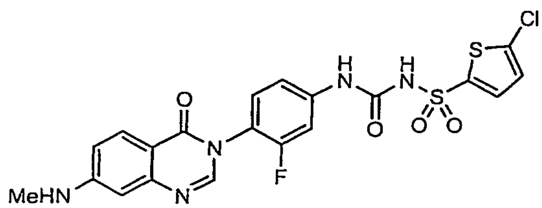
Example 942



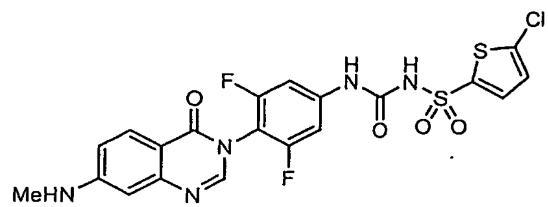
Example 943



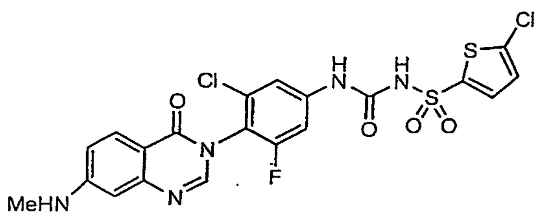
Example 944



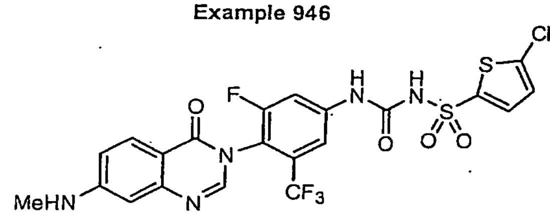
Example 945



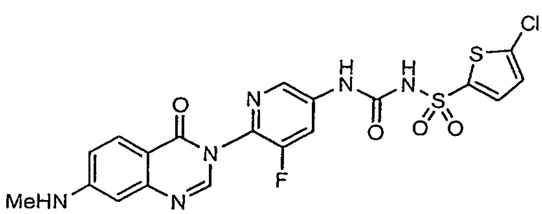
Example 946



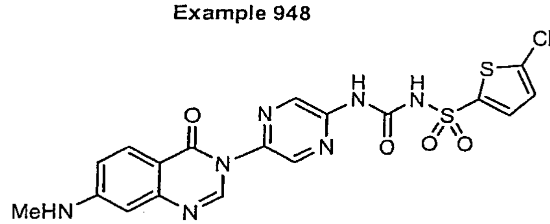
Example 947



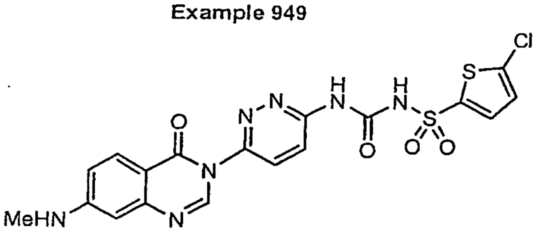
Example 948



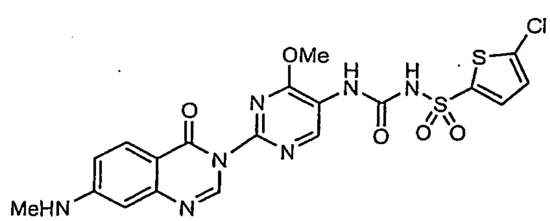
Example 949



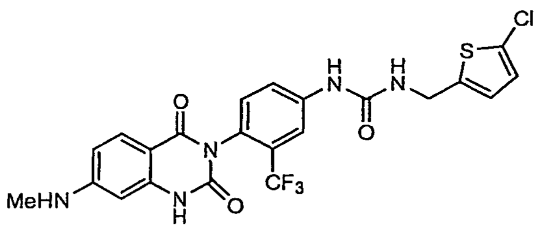
Example 950



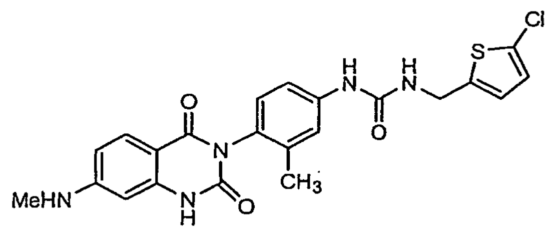
Example 951



Example 952



Example 953



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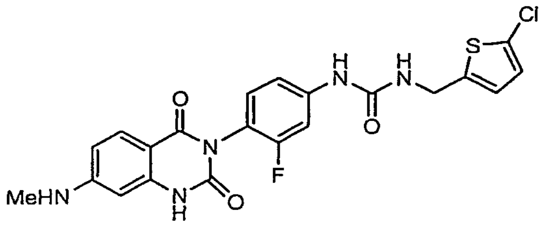
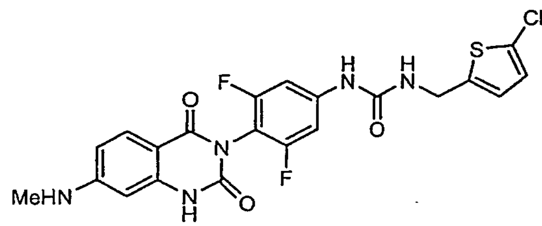
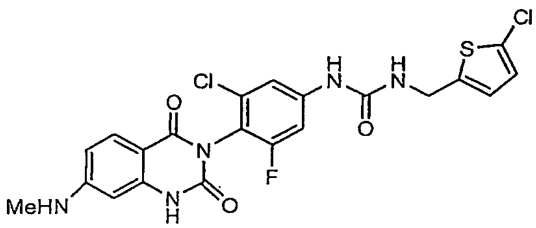


Example 955



Example 956



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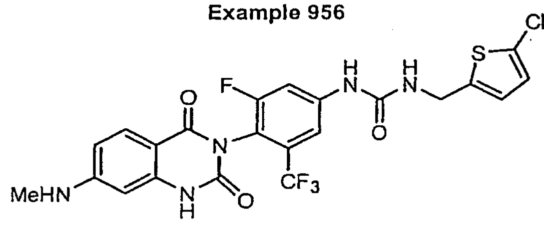
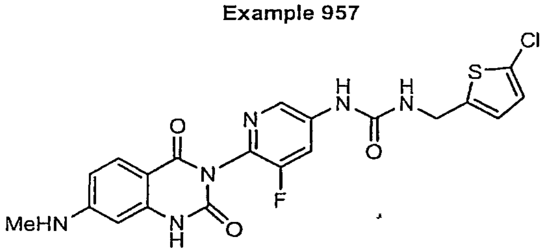
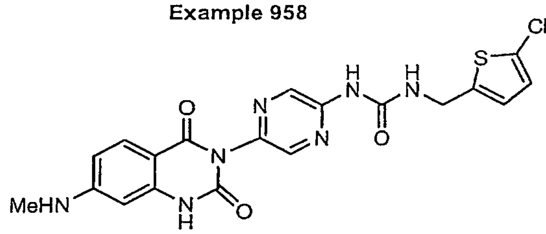


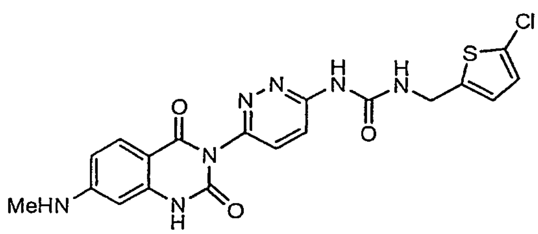
Example 958



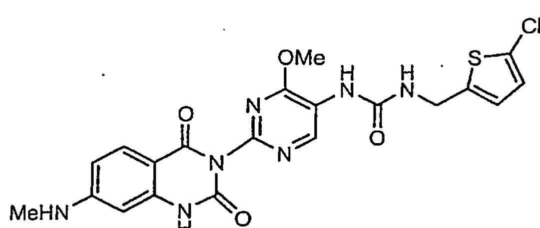
Example 959



Example 960



Example 961



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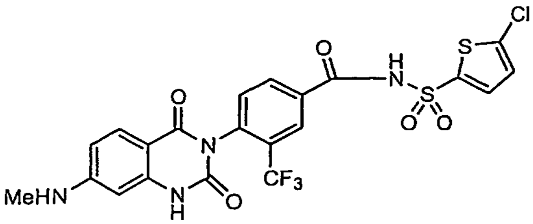

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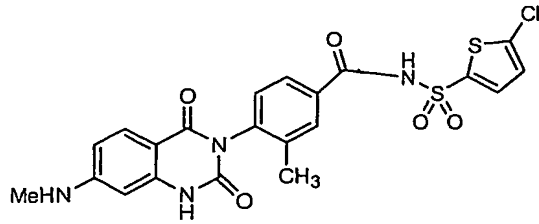

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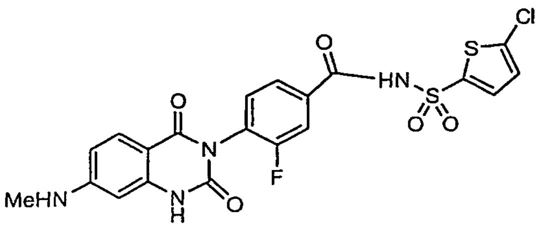
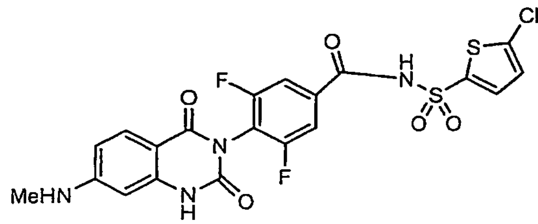
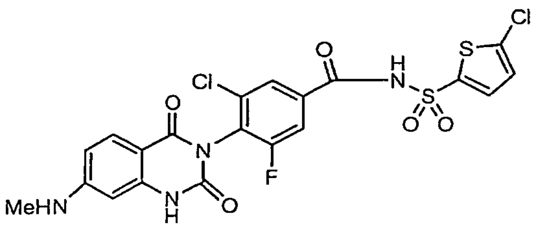

Example 965


Example 966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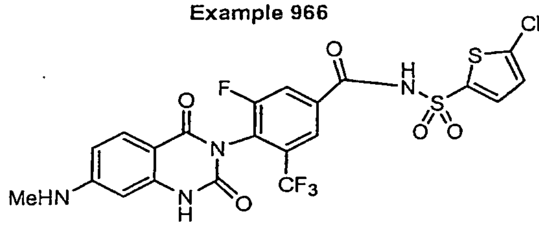
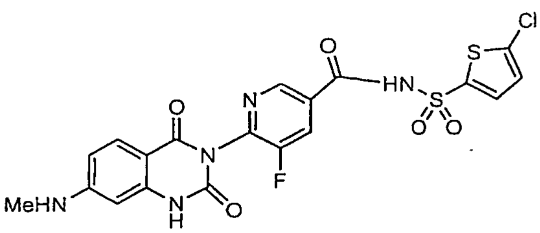
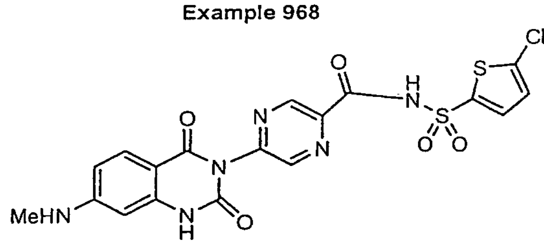
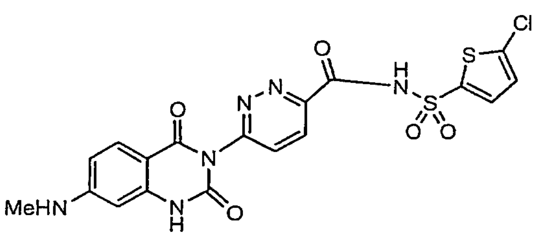
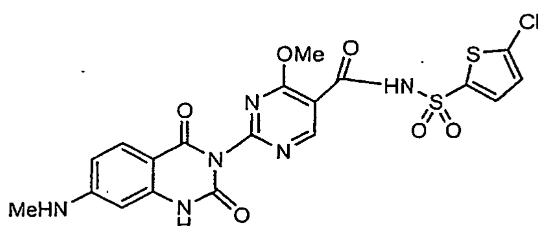
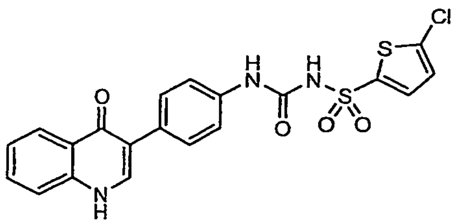

Example 968


Example 969

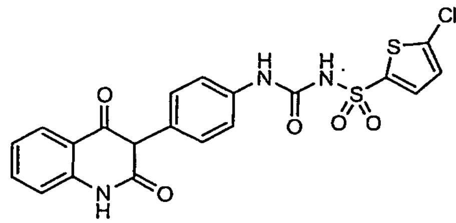

Example 970


Example 971

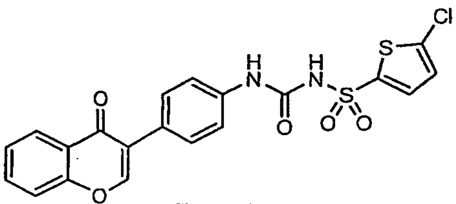

Example 972



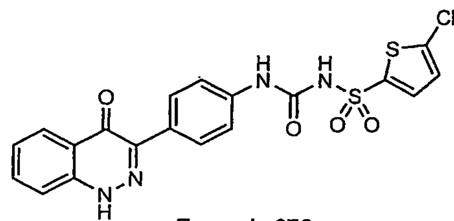
Example 973



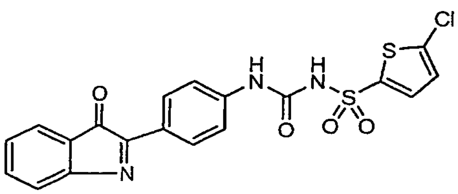
Example 974



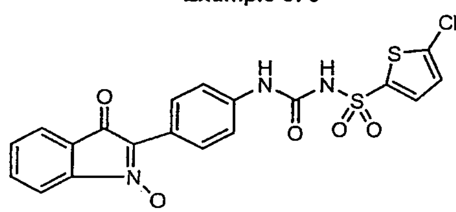
Example 975



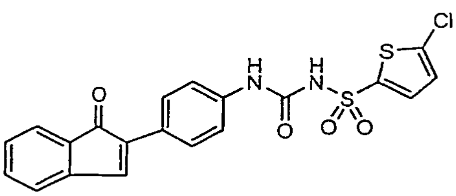
Example 976



Example 977



Example 978



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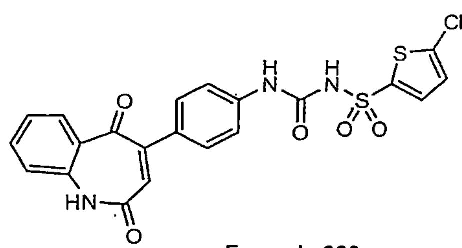
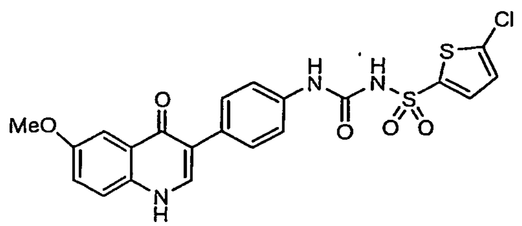
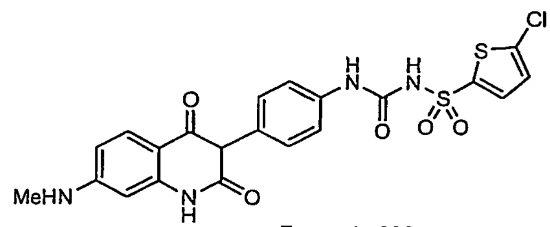


Example 980



Example 981



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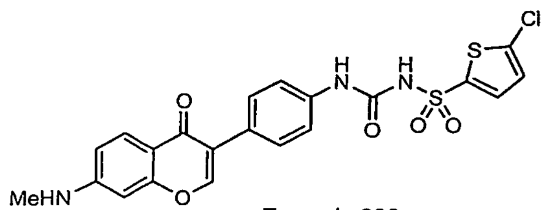
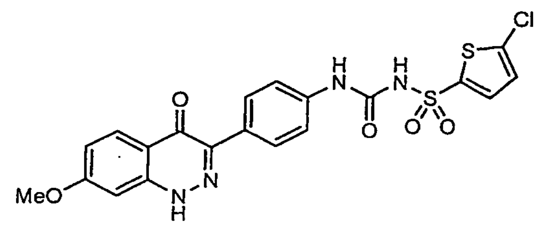


Example 983



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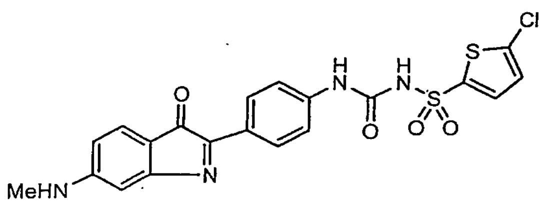
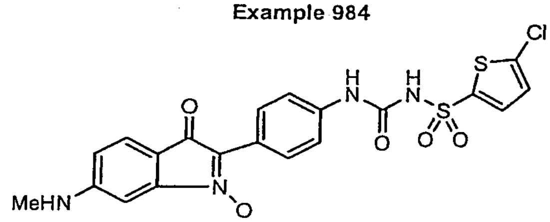
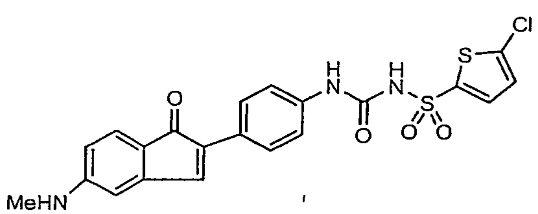


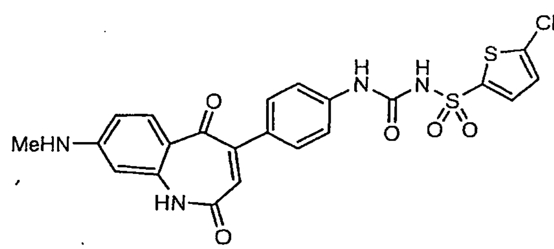
Example 985



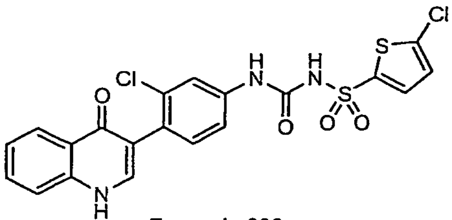
Example 986



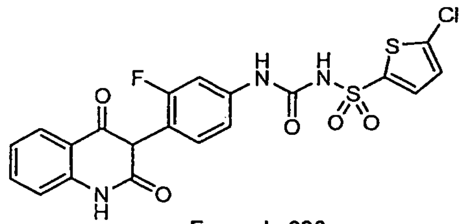
Example 987



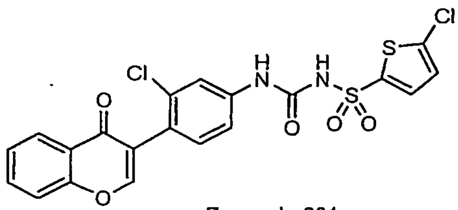
Example 988



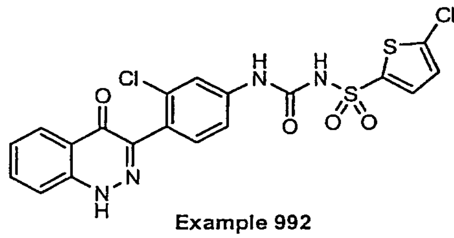
Example 989



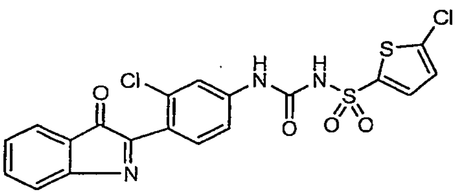
Example 990



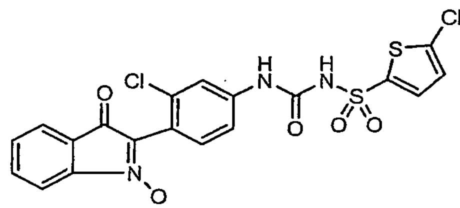
Example 991



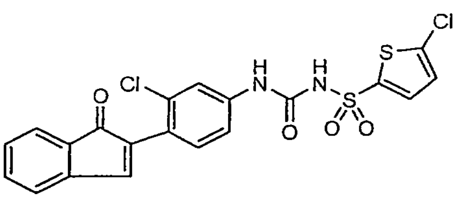
Example 992



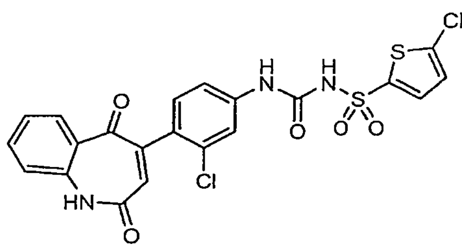
Example 993



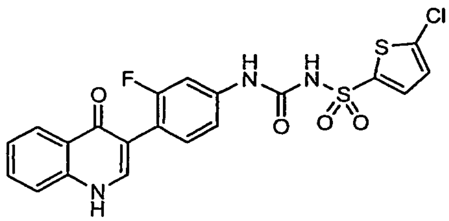
Example 994



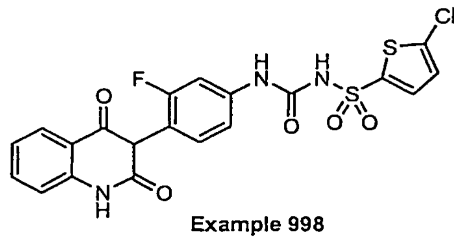
Example 995



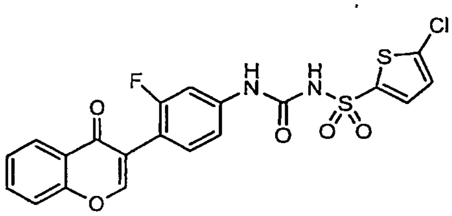
Example 996



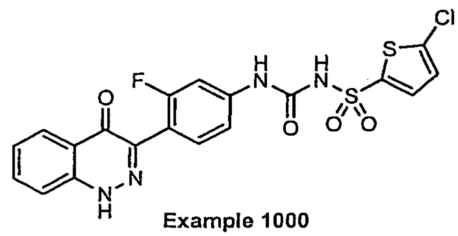
Example 997



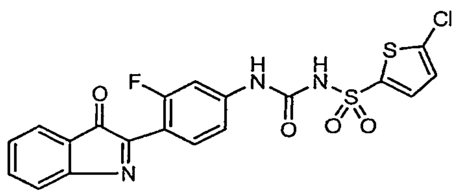
Example 998



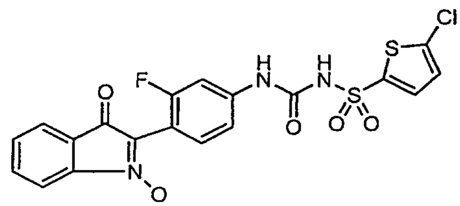
Example 999



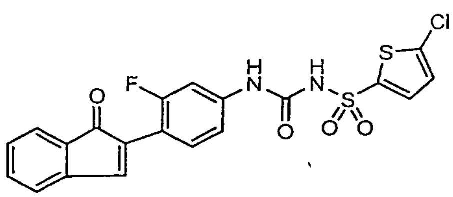
Example 1000



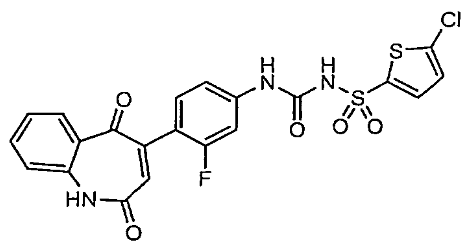
Example 1001



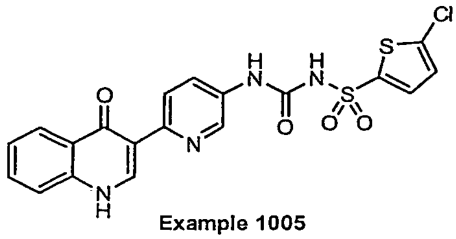
Example 1002



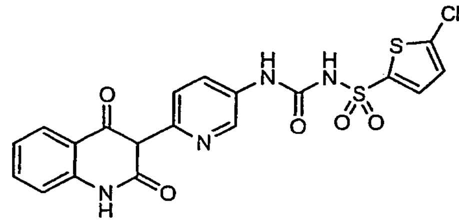
Example 1003



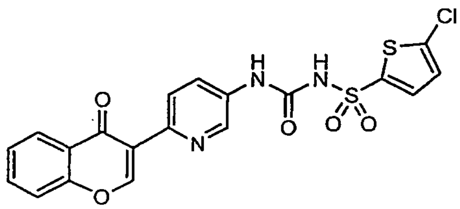
Example 1004



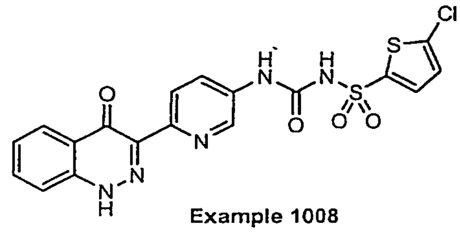
Example 1005



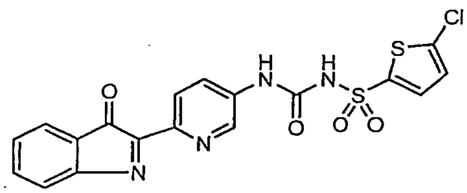
Example 1006



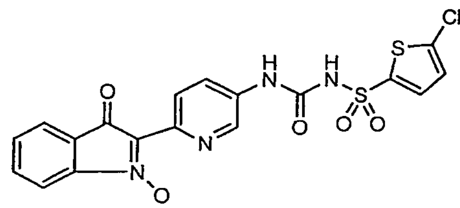
Example 1007



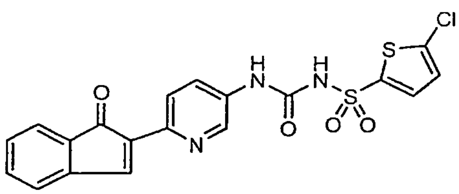
Example 1008



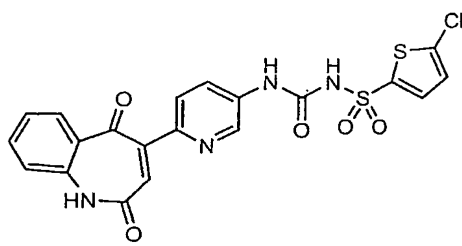
Example 1009



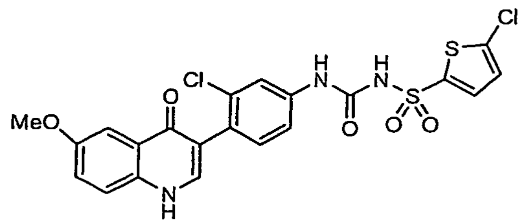
Example 1010



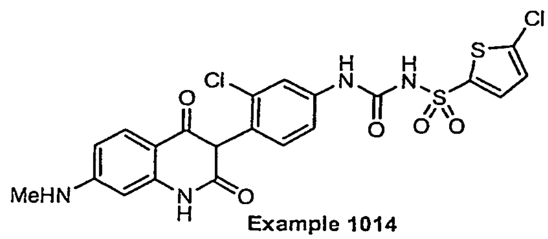
Example 1011



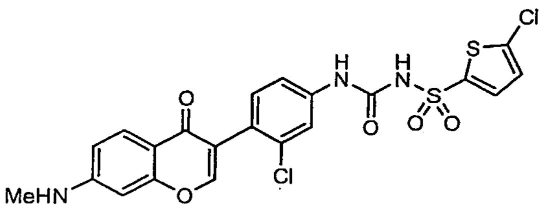
Example 1012



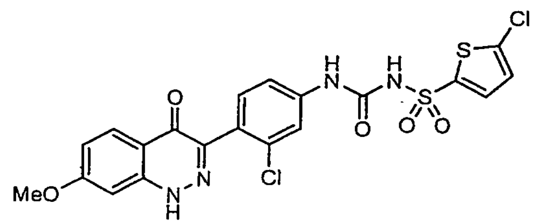
Example 1013



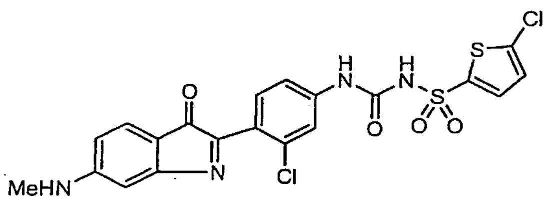
Example 1014



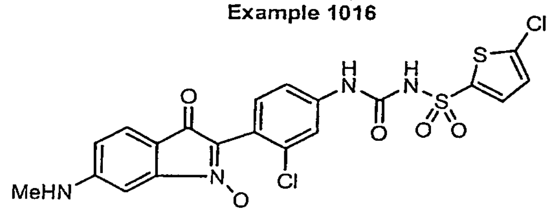
Example 1015



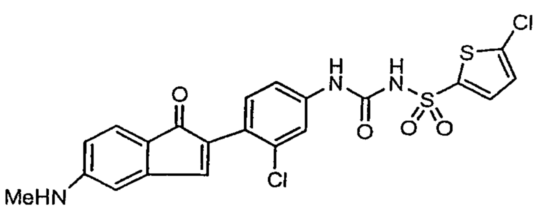
Example 1016



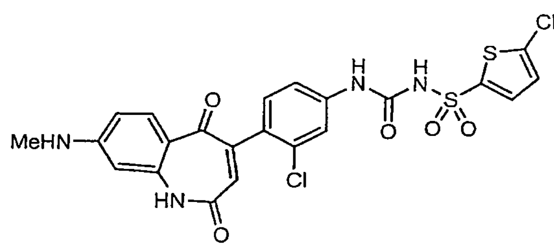
Example 1017



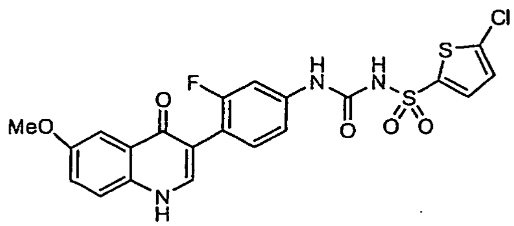
Example 1018



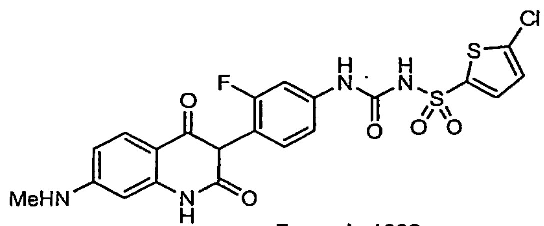
Example 1019



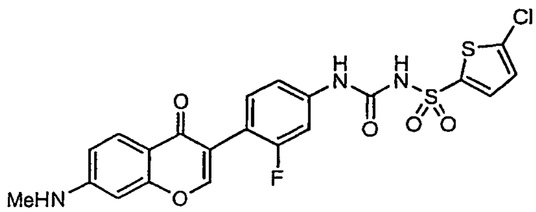
Example 1020



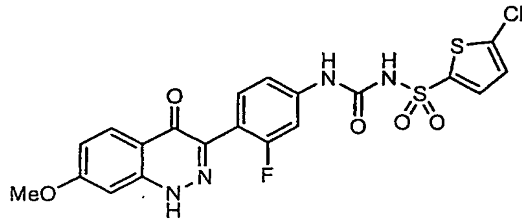
Example 1021



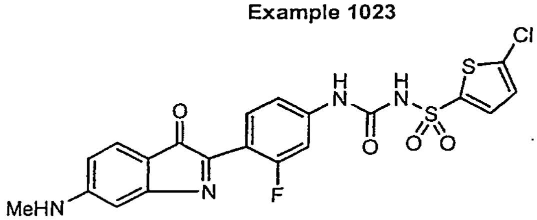
Example 1022



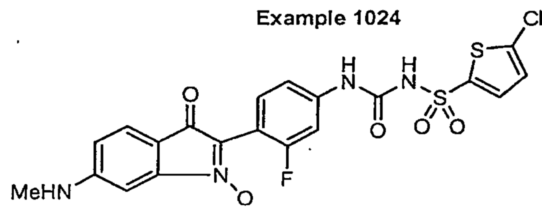
Example 1023



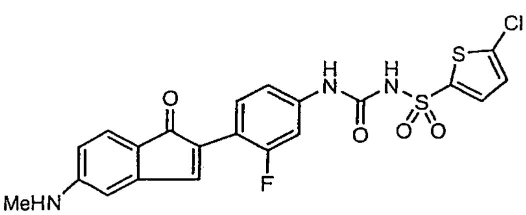
Example 1024



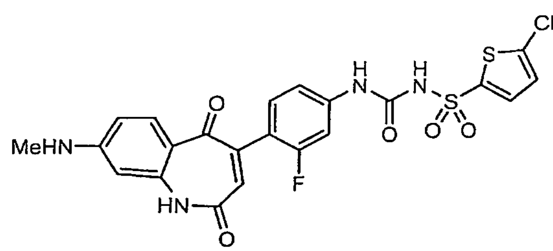
Example 1025



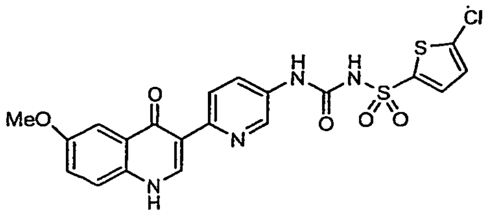
Example 1026



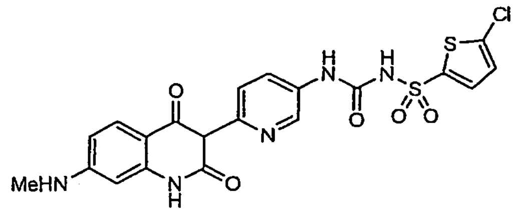
Example 1027



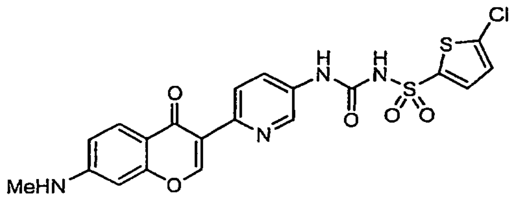
Example 1028



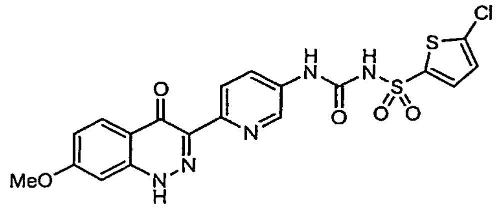
Example 1029



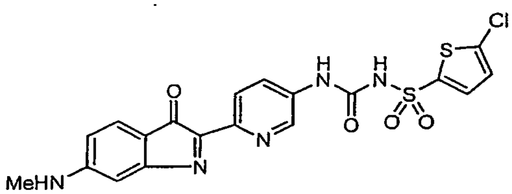
Example 1030



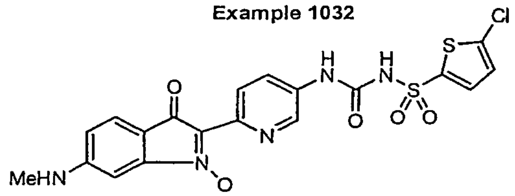
Example 1031



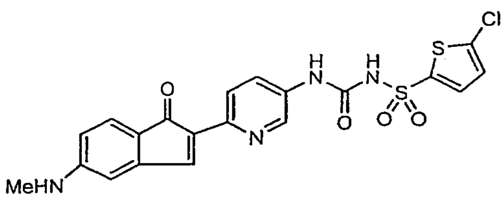
Example 1032



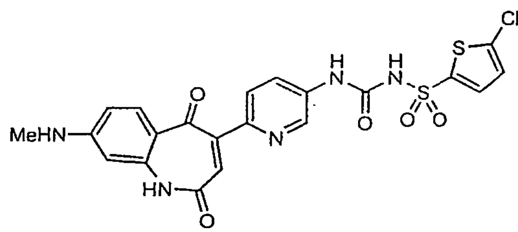
Example 1033



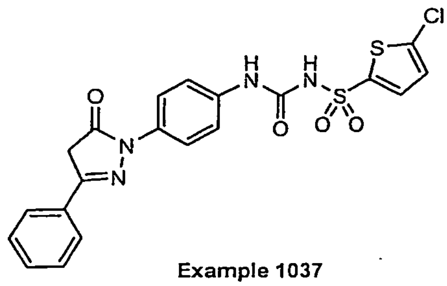
Example 1034

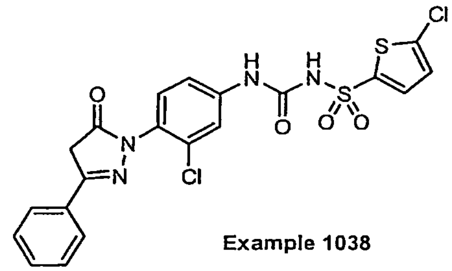


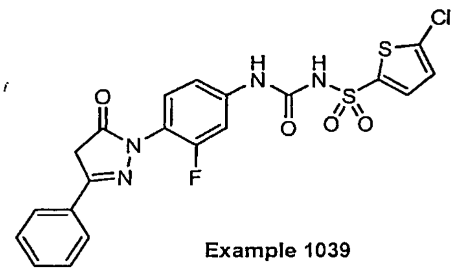
Example 1035

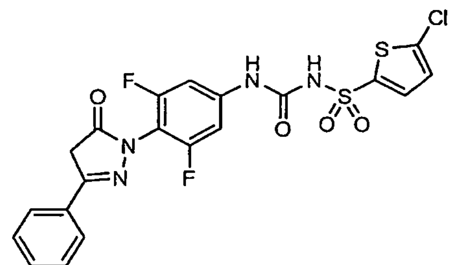


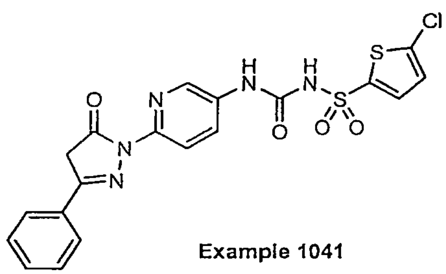
Example 1036

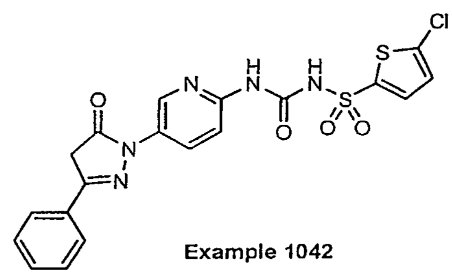

Example 1037

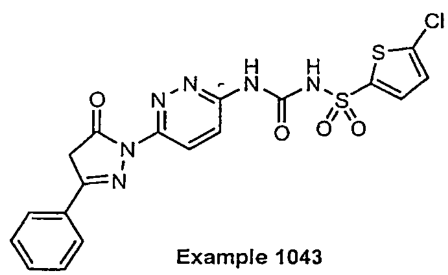

Example 1038

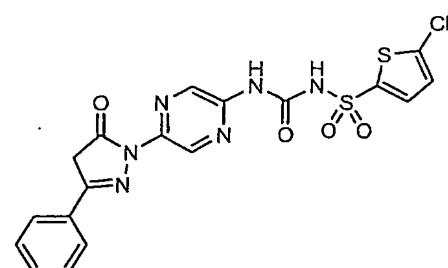

Example 1039

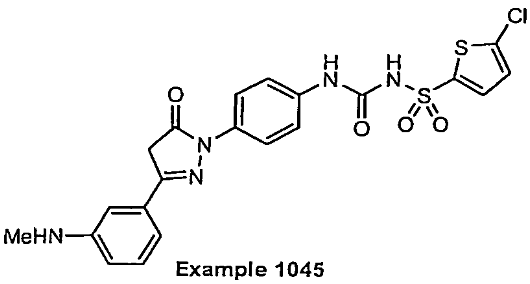

Example 1040


Example 1041

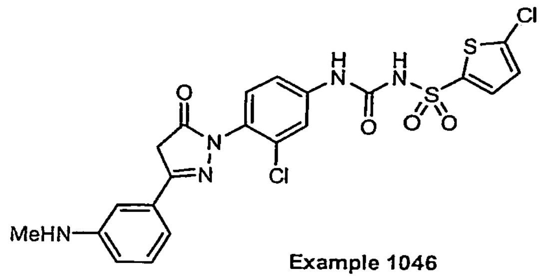

Example 1042


Example 1043

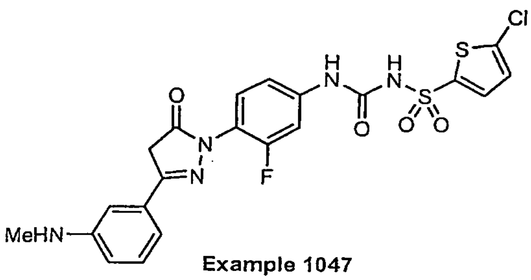

Example 1044



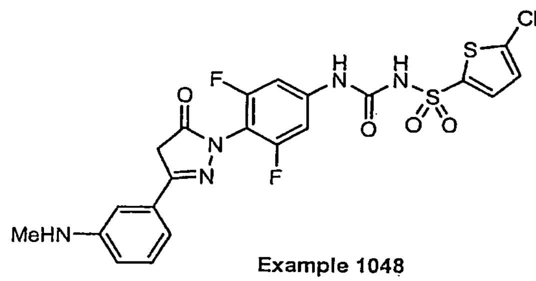
Example 1045



Example 1046



Example 1047



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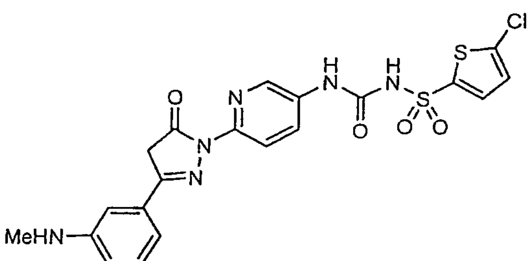
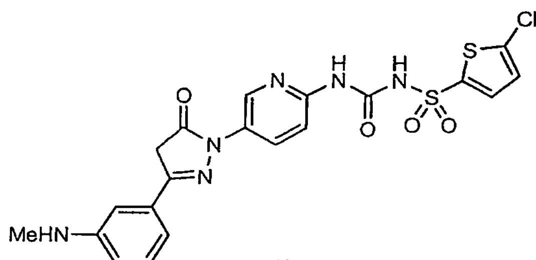
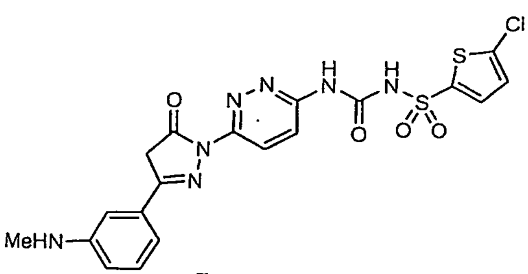


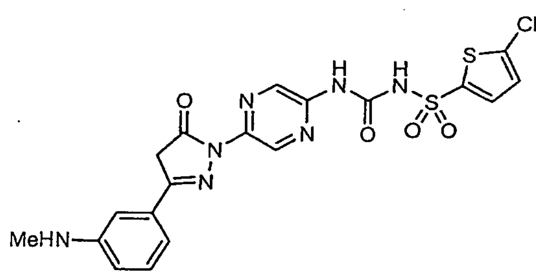
Example 1049



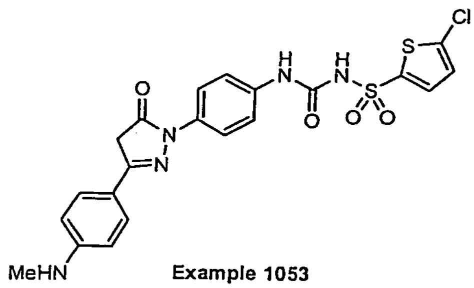
Example 1050



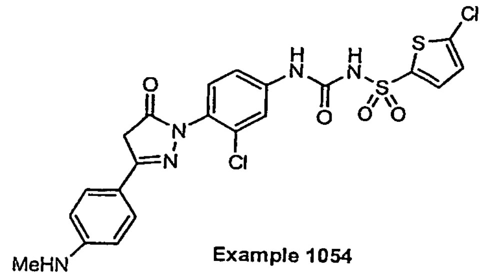
Example 1051



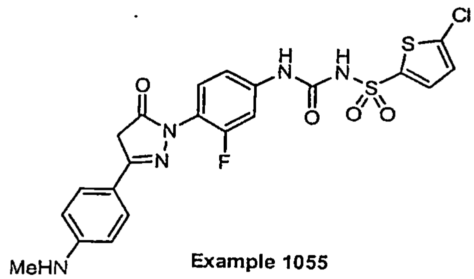
Example 1052



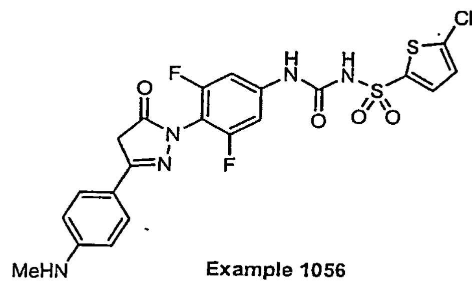
Example 1053



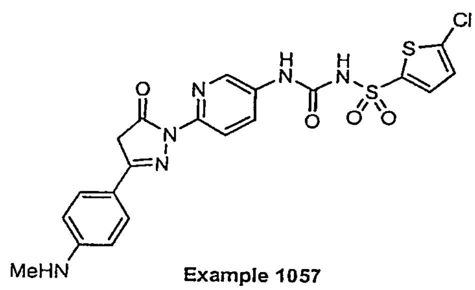
Example 1054



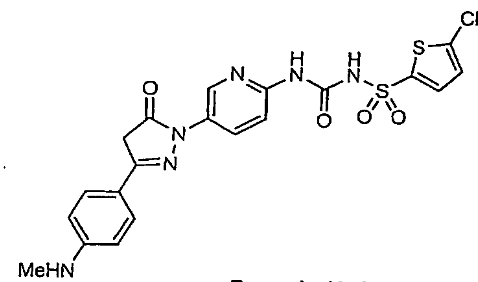
Example 1055



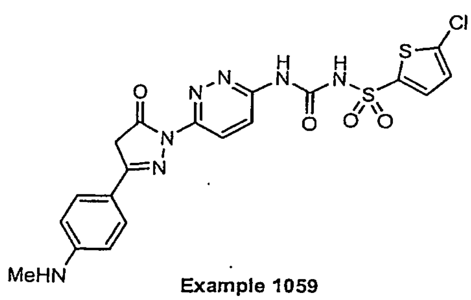
Example 1056



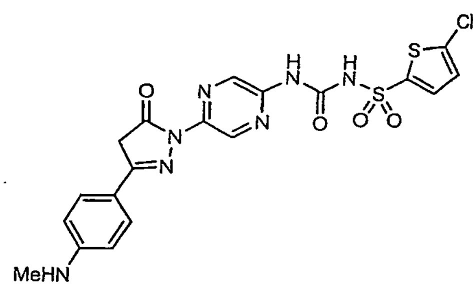
Example 1057



Example 1058



Example 1059



Example 1060

Preparation of Compounds of the Invention

A compound of formulae (I)-(VIII) may be prepared by various methods as outlined in the following documents: J. Med. Chem., 33, 23-93-2407 (1990); Biorg. & Med. Chem. Letts., Vol. 2, No. 9, pp. 987-992 (1992); J. Med. Chem., 35, 3012-3016 (1992); U.S. Patent 5,234,955 (1993), U.S. Patent 5,354,778 (1994); U.S. Patent 5,565,494 (1996); U.S. 5,594,028 (1997); U.S. Patent 5,302,724 (1994); and WO 97/08145, which are incorporated herein in their entirety by reference. Other well-known heterocyclic and carbocyclic synthetic procedures as well as modification of the procedures that are incorporated above may be utilized.

Compounds of formulae (I)-(VIII) may be isolated using typical isolation and purification techniques known in the art, including, for example, chromatographic and recrystallization methods.

In compounds of formula formulae (I)-(VIII) of the invention, carbon atoms to which four non-identical substituents are bonded are asymmetric. Accordingly, a compound of formulae (I)-(VIII) may exist as enantiomers, diastereomers or a mixture thereof. The enantiomers and diastereomers may be separated by chromatographic or crystallization methods, or by other methods known in the art. The asymmetric carbon atom when present in a compound of formulae (I)-(VIII) of the invention, may be in one of two configurations (R or S) and both are within the scope of the invention. The presence of small amounts of the opposing enantiomer or diastereomer in the final purified product does not affect the therapeutic or diagnostic application of such compounds.

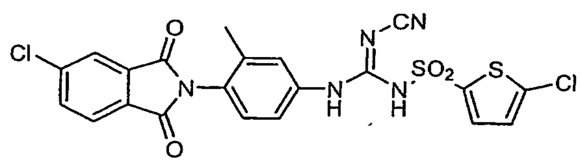
According to the invention, compounds of formulae (I)-(VIII) may be further treated to form pharmaceutically acceptable salts. Treatment of a compound of the invention with an acid or base may form, respectively, a pharmaceutically acceptable acid addition salt and a pharmaceutically acceptable base addition salt, each as defined above. Various inorganic and organic acids and bases known in the art including those defined herein may be used to effect the conversion to the salt.

The invention also relates to pharmaceutically acceptable isomers, hydrates, and solvates of compounds of formulae (I)-(VIII). Compounds of formulae (I)-(VIII) may

also exist in various isomeric and tautomeric forms including pharmaceutically acceptable salts, hydrates and solvates of such isomers and tautomers.

This invention also encompasses prodrug derivatives of the compounds of formulae (I)-(VIII). The term "prodrug" refers to a pharmacologically inactive derivative of a parent drug molecule that requires biotransformation, either spontaneous or enzymatic, within the organism to release the active drug. Prodrugs are variations or derivatives of the compounds of formulae (I)-(VIII) of this invention which have groups cleavable under metabolic conditions. Prodrugs become the compounds of the invention which are pharmaceutically active *in vivo* when they undergo solvolysis under physiological conditions or undergo enzymatic degradation. Prodrug compounds of this invention may be called single, double, triple, etc., depending on the number of biotransformation steps required to release the active drug within the organism, and indicating the number of functionalities present in a precursor-type form. Prodrug forms often offer advantages of solubility, tissue compatibility, or delayed release in the mammalian organism (Bundgard, *Design of Prodrugs*, pp. 7-9, 21-24, Elsevier, Amsterdam (1985); Silverman, *The Organic Chemistry of Drug Design and Drug Action*, pp. 352-401, Academic Press, San Diego, CA (1992)). Prodrugs commonly known in the art include acid derivatives well known to practitioners of the art, such as, for example, esters prepared by reaction of the parent acids with a suitable alcohol, or amides prepared by reaction of the parent acid compound with an amine, or basic groups reacted to form an acylated base derivative. Moreover, the prodrug derivatives of this invention may be combined with other features herein taught to enhance bioavailability.

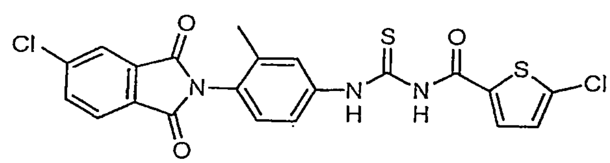
Example 1



Preparation of 5-chloro-2-{4-[({[(5-chloro(2-thienyl)) sulfonyl]amino}(cyanoimino)methyl)amino]-2-methylphenyl}benzo[c]azolidine-1,3-dione

A solution of N-(4-amino-2-methylphenyl)-4-chlorophthalimide (0.14 g, 0.5 mmol) and dimethyl N-cyanodithioiminocarbonate (0.13 g, 1 mmol) in pyridine (1.3 mL) was stirred at 115 °C for 8 hr. The reaction mixture was then cooled and concentrated in vacuo. To a solution of this crude intermediate (56 mg, 0.11 mol) in pyridine (0.7 mL) was added DBU (33 μL, 0.22 mmol) and 5-chlorothiophene-2-sulfonamide (44 mg, 0.22 mmol). The reaction mixture was heated at 115 °C for 23 hr with addition of DMAP (10 mg) after 2 hr. Acidification and HPLC purification yielded (2Z)-2-aza-3-{[(5-chloro(2-thienyl))sulfonyl]amino}-3-{[4-(5-chloro-1,3-dioxobenzo[c]azolidin-2-yl)-3-methylphenyl]amino}prop-2-enenitrile (14 mg, 24%). ES-MS (M+H)+ = 534, 536 (Cl). ^{1}H-NMR (DMSO-d_6): δ 2.03 (s, 3H), 7.06-7.07 (d, 1H), 7.18-7.20 (d, 1H), 7.30-7.31 (d, 1H), 7.37 (s, 2H), 7.93-7.94 (2H), 8.03 (d, 1H), 8.84 (s, 1H).

Example 1061



Preparation of (5-chloro(2-thienyl))-N-({[4-(5-chloro-1,3-dioxobenzo[c]azolin-2-yl)-3-methylphenyl]amino}thioxomethyl)carboxamide

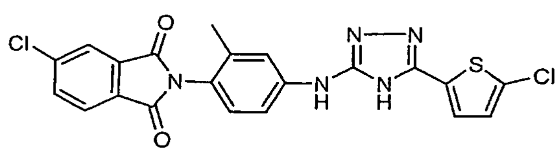
A. Synthesis of 5-chlorothiophene-2-carbonyl chloride

To a chilled solution of 5-chlorothiophene-2-carboxylic acid (0.16 g, 1.0 mmol) in EtOAc (3 mL) and DMF (1 drop) was added neat oxalyl chloride (92 μL, 1.05 mmol). The reaction mixture was stirred cold for 2 hr and concentrated in vacuo to give crude 5-chlorothiophene-2-carbonyl chloride.

B. Synthesis of (5-chloro(2-thienyl))-N-({[4-(5-chloro-1,3-dioxobenzo[c]azolin-2-yl)-3-methylphenyl]amino}thioxomethyl)carboxamide

To a suspension of KSCN (29 mg, 0.3 mmol) in dry acetonitrile (0.2 mL) was added a solution of the crude acid chloride (36 mg, 0.2 mmol) in CH_3CN (0.2 mL). The resulting suspension was stirred at room temp for 30 min. This acylthioisocyanate in situ was added to a suspension of N-(4-amino-2-methylphenyl)-4-chlorophthalimide (58 mg, 0.2 mmol) in CH_3CN. The reaction mixture was stirred at room temp for 1 hr, filtered and dried to give pure (5-chloro-(2-thienyl))-N-({[4-(5-chloro-1,3-dioxobenzo[c]azolin-2-yl)-3-methylphenyl]amino}thioxomethyl)carboxamide (66 mg, 70%). ES-MS (M+H)+ = 490, 492 (Cl).

Example 1062

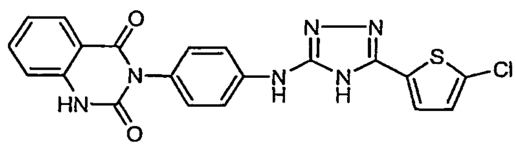


Preparation of 5-chloro-2-(4-{[5-(5-chloro(2-thienyl))(4H-1,2,4-triazol-3-yl)]amino}-2-methylphenyl)benzo[c]azoline-1,3-dione

To a suspension of (5-chloro(2-thienyl))-N-({[4-(5-chloro-1,3-dioxobenzo[c]azolin-2-yl)-3-methylphenyl]amino}thioxomethyl)carboxamide (15 mg, 0.030 mmol) and hydrazine dihydrochloride (4 mg, 0.038 mmol) in DMF (0.3 mL) was added HgO (7 mg, 0.032 mmol). The reaction was stirred at room temp for 17 hr, and HPLC purified to give the desired product 5-chloro-2-(4-{[5-(5-chloro(2-thienyl))(4H-

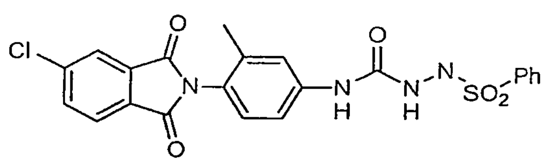
1,2,4-triazol-3-yl)]amino}-2-methylphenyl)benzo[c]azoline-1,3-dione (2 mg) (ES-MS (M+H)+ = 470, 472) and the aminoguanidine intermediate N-((1E)-2-aza-1-{[4-(5-chloro-1,3-dioxobenzo[c]azolidin-2-yl)-3-methylphenyl]amino}-2-aminovinyl)(5-chloro(2-thienyl))carboxamide (2 mg) ES-MS (M+H)+ = 488, 490 (2Cl).

Example 1063



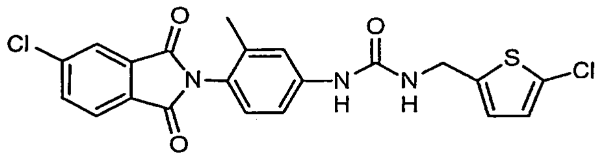
Preparation of 3-(4-{[5-(5-chloro-2-thienyl)-4H-1,2,4-triazol-3-yl]amino}phenyl)-1,3-dihydroquinazoline-2,4-dione was executed using the same methodology as shown in Examples 1061 and 1062, using 3-(4-aminophenyl)-1,3-dihydroquinazoline-2,4-dione as the aniline in step B from Example 1061. ES-MS (M+H)+ = 437, 439 (Cl).

Example 1064



To a solution of triphosgene (22 mg, 0.074 mmol) in CH_2Cl_2 (1 mL) was added a suspension of N-(4-amino-2-methylphenyl)-4-chlorophthalimide (57 mg, 0.2 mmol) in CH_2Cl_2 (1.5 mL) and diethylisopropylamine (70 µL) dropwise over 10 min. The reaction mixture was stirred for 10 min, then a suspension of benzenesulfonylhydrazide (52 mg, 0.3 mmol) in CH_2Cl_2 (1.5 mL) and DIEA (35 µL) was added. The mixture was stirred at room temp for 17 hr, acidified and HPLC purified to give N-[4-(5-chloro-1,3-dioxobenzo[c]azolidin-2-yl)-3-methylphenyl][2-(phenylsulfonyl)hydrazino]-carboxamide (43 mg, 46%). ES-MS (M+H)+ = 485, 487. ^{1}H-NMR (DMSO-d_6): δ 2.00 (s, 3H), 7.13-7.15 (d, 1H), 7.28-7.31 (d, 1H), 7.34 (s, 1H), 7.55-7.67 (m, 3H), 7.82-7.84 (m, 2H), 7.93 (s, 2H), 8.02 (s, 1H).

Example 1065



Preparation of {[(5-chloro(2-thienyl))methyl]amino}-N-[4-(5-chloro-1,3-dioxobenzo[c]azolidin-2-yl)-3-methylphenyl]carboxamide

A. Synthesis of 5-chloro-2-[(1,3,5,7-tetraazatricyclo[3.3.1.1(3,7)] decyl)methyl]thiophene

To a suspension of hexamethylenetetramine (HMTA) (3.12 g, 22.2 mmol) in $CHCl_3$ (35 mL) was added 2-chloro-5-chloromethylthiophene (1.02 mL, 8.46 mmol). The reaction mixture was heated at reflux for 4 hr, cooled, and filtered to give white solid 5-chloro-2-[(1,3,5,7-tetraazatricyclo-[3.3.1.1(3,7)]decyl) methyl]thiophene (2.28 g, 88%). ES-MS (M)+ = 271, 273 (Cl). ^{1}H-NMR (DMSO-d_6): δ 4.27 (s, 2H), 4.39-4.57 (ABq, 6H), 5.06 (s, 6H), 7.21-7.24 (ABq, 2H).

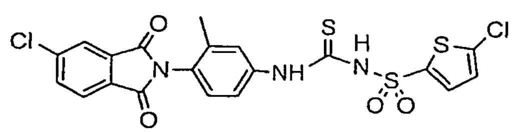
B. Synthesis of (5-chloro-2-thienyl)methylamine

To a solution of 5-chloro-2-[(1,3,5,7-tetraazatricyclo[3.3.1.1(3,7)] decyl)methyl]thiophene (2.15 g, 7 mmol) in methanol (10 mL) and water (5 mL) was added conc. HCl (5 mL). The reaction mixture was refluxed for 3 hr, poured onto water and washed with ethyl ether. The aqueous layer was basified with 4N NaOH and extracted into ethyl ether, washed with brine, dried and concentrated in vacuo to give (5-chloro-2-thienyl)methylamine (0.8 g, 78%).

C. Synthesis of {[(5-chloro(2-thienyl))methyl]amino}-N-[4-(5-chloro-1,3-dioxobenzo[c]azolidin-2-yl)-3-methylphenyl]carboxamide

To a solution of triphosgene (22 mg, 0.074 mmol) in CH_2Cl_2 (1 mL) was added suspension of N-(4-amino-2-methylphenyl)-4-chlorophthalimide (57 mg, 0.2 mmol) in CH_2Cl_2 (1.5 mL) and diethylisopropylamine (70 μL) dropwise over 10 min. The reacti mixture was stirred for 10 min, then a solution (5-chloro-2-thienyl)methylamine from step B (47 mg, 0.32 mmol) in CH_2Cl_2 (1 mL) and DIEA (35 μL) was added. The mixtu was stirred at room temp for 17 hr, acidified and HPLC purified to give {[(5-chloro(2-thienyl))methyl]amino}-N-[4-(5-chloro-1,3-dioxobenzo[c]azolidin-2-yl)-3-methylphenyl]carboxamide (18 mg, 20%). ES-MS (M+H)+ = 460, 462 (Cl). ^{1}H-NMR (DMSO-d_6): δ 2.02 (s, 3H), 4.34-4.36 (d, 2H), 6.77-6.80 (t, 1H), 6.82-6.93 (2d, 2H), 7.14-7.16 (d, 1H), 7.29-7.32 (dd, 1H), 7.41 (d, 1H), 7.93 (ABq, 2H), 8.02 (s, 1H), 8.77 (s 1H).

Example 1066



Preparation of 5-chloro-2-{4-[({[(5-chloro(2-thienyl))sulfonyl]amino}thioxomethyl) amino]-2-methylphenyl}benzo[c]azolidine-1,3-dione:

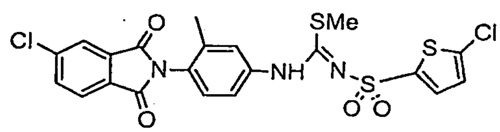
A. Synthesis of 4-(5-chloro-1,3-dioxobenzo[c]azolidin-2-yl)-3-methylbenzenisothiocyanate

To a slurry of 150 mg (0.52 mmol) of 2-(4-amino-2-methylphenyl)-5-chlorobenzo[c]azoline-1,3-dione in 2 mL of acetone, was added 41 uL (0.54 mmol) of thiophosgene. The yellow slurry dissolved whereupon a white precipitate formed. After 1h, this solid was collected by filtration and dried to give 127 mg (74%) of the desired product.

B. Synthesis of 5-chloro-2-{4-[({[(5-chloro(2-thienyl))sulfonyl]amino} thioxomethyl)amino]-2-methylphenyl}benzo[c]azolidine-1,3-dione

To a slurry of 51 mg (0.156 mmol) of the isothiocyanate prepared above and 31 mg (0.156 mmol) of 5-chlorothiophenesulfonamide in 300 µL of DMSO was added 26 µL of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). After a few minutes the reaction mixture was diluted with 1.2 mL of water and acidified with acetic acid to pH 4 when a precipitate was formed, collected , and dried to give 77 mg (94%) of the titled compound. ES-MS (M+H)+ = 525.8 (2Cl).

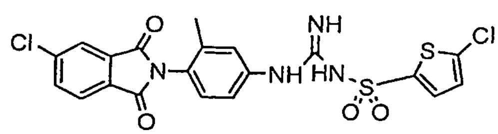
Example 1067



Preparation of 2-[4-({(1Z)-2-aza-2-[(5-chloro(2-thienyl))sulfonyl]-1-methylthiovinyl}amino)-2-methylphenyl]-5-chlorobenzo[c]azolidine-1,3-dione:

To a solution of 20 mg (0.038 mmol) 5-chloro-2-{4-[({[(5-chloro(2-thienyl))sulfonyl]amino} thioxomethyl)amino]-2-methylphenyl}benzo[c]azolidine-1,3-dione in 780 µL of acetone and 63 µL of 0.6M $NaHCO_3$ was added 5.9 µL of methyl iodide. After 2h, the reaction mixture was acidified with acetic acid and the precipitate was collected and dried to give 13 mg (63%) of the titled compound.

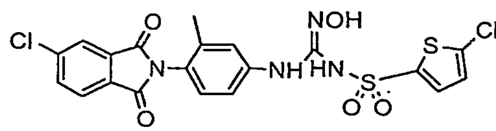
Example 1068



Preparation of 5-chloro-2-{4-[({[(5-chloro(2-thienyl))sulfonyl]amino}iminomethyl) amino]-2-methylphenyl}benzo[c]azolidine-1,3-dione

A 15 mg portion of the 5-chloro-2-{4-[({[(5-chloro(2-thienyl))sulfonyl]amino}thioxomethyl)-amino]-2-methylphenyl}benzo[c]azolidine-1,3-dione was dissolved in 120 μL of DMF containing 6.6 mg of conc. ammonium hydroxide and 6 mg of mercuric oxide was added. After stirring for 18 h, the mercuric sulfide was filtered off and the solution was purified by reversed phase HPLC to give 1 mg (7%) of a white solid. ES-MS (M+H)+ = 509 (2Cl).

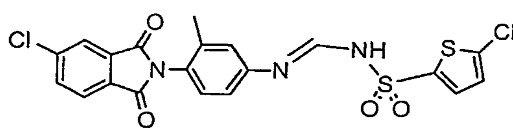
Example 1069



Preparation of 5-chloro-2-{4-[({[(5-chloro(2-thienyl))sulfonyl]amino}(hydroxyimino)methyl)amino]-2-methylphenyl}benzo[c]azolidine-1,3-dione

The titled compound was prepared in a similar fashion as for Example 1068 with a 10% yield after purification. ES-MS (M+H)+ = 525 (2Cl).

Example 1070



Preparation of 5-chloro-2-{4-[({[(5-chloro(2-thienyl))sulfonyl]amino}methyl)amino]-2-methylphenyl}benzo[c]azolidine-1,3-dione

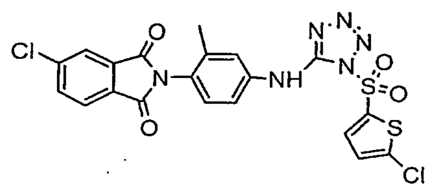
A. Synthesis of 2-[4-((1E)-1-aza-2-ethoxyvinyl)-2-methylphenyl]-5-chlorobenzo[c]azolidine-1,3-dione

A 50 mg (0.175 mmol) portion of 2-(4-amino-2-methylphenyl)-5-chlorobenzo[c]azoline-1,3-dione in 2 mL of triethylorthoformate was heated to reflux for 1h then distilled to leave a solid, 598 mg (100%).

B Synthesis of 5-chloro-2-{4-[({[(5-chloro(2-thienyl))sulfonyl]amino}methyl)amino]-2-methylphenyl}benzo[c]azolidine-1,3-dione

A 100 mg sample of 2-[4-((1E)-1-aza-2-ethoxyvinyl)-2-methylphenyl]-5-chlorobenzo[c]-azolidine-1,3-dione plus 58 mg (0.29 mmol) of 5-chlorothiophenesulfonamide was slurried in 1.2 mL of MeOH, heated to reflux for 2h, and the methanol was distilled off. The remaining solid was triturated with ACN/MeOH, filtered, and concentrated to afford 104 mg (87%) of the titled compound. ES-MS (M+H)+ = 494.

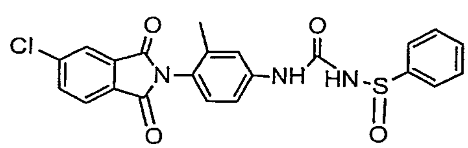
Example 1071



Preparation of 5-chloro-2-[4-({1-[(5-chloro(2-thienyl))sulfonyl](1,2,3,4-tetraazol-5-yl)}amino)-2-methylphenyl]benzo[c]azolidine-1,3-dione

The titled compound was prepared in a similar fashion as for Example 1068 to yield a 18% yield after RP-HPLC purification. ES-MS (M+H)+ = 535 (2Cl).

Example 1072



5-chloro-2-[4-({1-[(5-chloro(2-thienyl))sulfonyl](1,2,3,4-tetraazol-5-yl)}amino)-2-methylphenyl]benzo[c]azolidine-1,3-dione

A. Synthesis of chlorophenylsulfoxide

To 2 g (12 mmol) of sodium benzenesulfinic acid was added 5 mL of thionyl chloride and stirred at 0 °C for 4 h. The product was isolated by bulb-to-bulb distillation (180 °C @ 4 mmHg) to afford 1.25g (64%) of the liquid benzenesulfinic chloride.

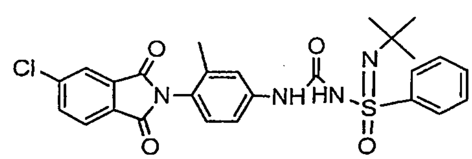
B. Synthesis of benzenesulfinamide

The chlorophenylsulfoxide (500 mg, 3.2 mmol) was dissolved in 5 mL of diethyl ether at 0 °C and anhydrous ammonia was bubbled through until no more precipitate is formed. The solution was filtered and concentrated to afford a solid which was recrystallized from water to afford 152 mg (35%) of benzenesulfinamide.

C. Synthesis of 5-chloro-2-[4-({1-[(5-chloro(2-thienyl))sulfonyl](1,2,3,4-tetraazol-5-yl)}amino)-2-methylphenyl]benzo[c]azolidine-1,3-dione

A 16 mg portion of benzenesulfinamide and 47 mg of 2-(4-amino-2-methylphenyl)-5-chlorobenzo[c]azoline-1,3-dione was dissolved in 232 uL of CAN followed by 18 μL of DBU. The reaction was stirred at 23 °C for 1h and purified by RP-HPLC to give 20 mg (38%) of the desired material. ES-MS (M+H)+ = 454 (2Cl).

Example 1073



Preparation of {[4-(5-chloro-1,3-dioxobenzo[c]azolidin-2-yl)-3-methylphenyl]amino}-N-(N-t-butylphenylsulfonimidoyl)carboxamide:

A. Synthesis of (tert-butyl)(phenylsulfonyl)amine

In a similar fashion for the preparation of Example 1072 B, tert-butyl amine (5 equivalents) was used to prepare the named compound in 75% yield. ^{1}H-NMR (DMSO-d_6): δ 7.67 (m,2); 7.45 (m,3) 4.83 (br s,1); 1.39 (s,9).

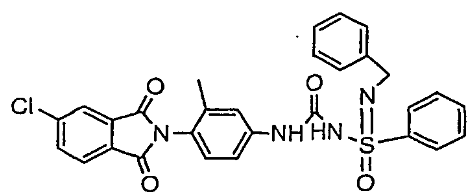
B. Synthesis of (tert-butyl)(phenyliminosulfonyl)amine

To a 50 mg-portion (0.25 mmol) of (tert-butyl)(phenylsulfonyl)amine in 5 mL of anhydrous THF was added 58 mg (0.26 mmol) of N-chlorosaccharin under an argon atmosphere. After a few minutes the reaction mixture was cooled to –78 °C, and anhydrous ammonia was bubbled through. After warming to 23 °C the solvent was evaporated, the residue was dissolved in water, extracted 3 times with EtOAc. The combined organic layers were washed with 5% $NaHCO_3$, dried (Na_2SO_4), and concentrated to afford 37 mg (68%) of the titled compound. ES-MS (M+H)+ = 236.

C. Synthesis of {[4-(5-chloro-1,3-dioxobenzo[c]azolidin-2-yl)-3-methylphenyl]amino}-N-(N-t-butylphenylsulfonimidoyl)carboxamide

In a similar fashion for preparation of Example 1072C, the titled compound was prepared in 2% yield after RP-HPLC purification. ES-MS (M+H)+ = 525.

Example 1074



Preparation of {[4-(5-chloro-1,3-dioxobenzo[c]azolidin-2-yl)-3-methylphenyl]amino}-N-(N-benzylphenylsulfonimidoyl)carboxamide

A. Synthesis of (benzyl)(phenylsulfonyl)amine

In a similar fashion for the preparation of Example 1072 Step B, benzylamine (5 equivalents) was used to prepare the named compound in 74% yield. ES-MS (M+H)+ = 232.1. ^{1}H-NMR ($CDCl_3$) δ 7.67 (m,2); 7.51 (m,3); 7.28 (m,5); 4.28 (ABX,1); 4.23 (ABX,1); 3.89 (X,1).

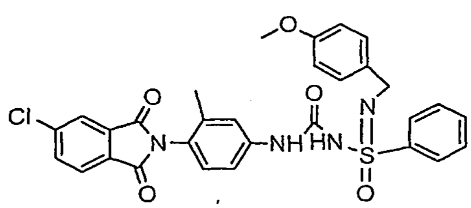
B. Synthesis of (benzyl)(phenyliminosulfonyl)amine

In a similar fashion as for the preparation of Example 1072 Step C, the titled compound was prepared in quantitative yield.

C. {[4-(5-chloro-1,3-dioxobenzo[c]azolidin-2-yl)-3-methylphenyl]amino}-N-(N-benzylphenylsulfonimidoyl)carboxamide

In a similar fashion for preparation of Example 1072 Step C, the titled compound was prepared in 34% yield after RP-HPLC purification. ES-MS (M+H)+ = 559.

Example 1075



Preparation of {[4-(5-chloro-1,3-dioxobenzo[c]azolidin-2-yl)-3-methylphenyl]amino}-N-(N-p-methoxybenzylphenylsulfonimidoyl)carboxamide

A. Synthesis of (p-methoxybenzyl)(phenyliminosulfonyl)amine

In a similar fashion for the preparation of Example 1072 Step B, p-methoxybenzylamine (5 equivalents) was used to prepare the named compound in 66%

yield. ES-MS (M+H)+ = 262. ^{1}H-NMR ($CDCl_3$): δ 7.97 (m, 2); 7.49 (m, 3); 7.18 (d, 2); 6.81 (d, 2); 4.20 (m, 2); 3.8 (dd, 1); 3.74 (s, 3).

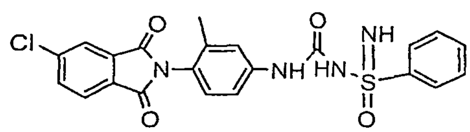
B. Synthesis of (p-methoxybenzyl)(phenyliminosulfonyl)amine

In a similar fashion as for the preparation of Example 1072 Step C, the titled compound was prepared in quantitative yield. Material used in next step without purification.

C. Synthesis of {[4-(5-chloro-1,3-dioxobenzo[c]azolidin-2-yl)-3-methylphenyl]amino}-N-(N-benzylphenylsulfonimidoyl)carboxamide

In a similar fashion for preparation of Example 1072 Step C, the titled compound was prepared in 17% yield after RP-HPLC purification. ES-MS (M+H)+ = 589.

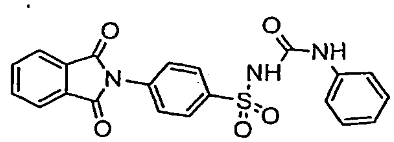
Example 1076



Preparation of {[4-(5-chloro-1,3-dioxobenzo[c]azolidin-2-yl)-3-methylphenyl] amino}-N-(phenylsulfonimidoyl)carboxamide

To 10 mg (0.016 mmol) of {[4-(5-chloro-1,3-dioxobenzo[c]azolidin-2-yl)-3-methylphenyl]-amino}-N-(N-p-methoxybenzylphenylsulfonimidoyl)carboxamide dissolved in 380 μL of CAN followed by 96 uL of water was added 70 mg (0.13 mmol) of cerric ammonium nitrate. After 20 m, the reaction was complete and purified by RP-HPLC to give 1.8 mg (23%) after lyophilization. ES-MS (M+H)+ = 469 (Cl).

Example 1077



Preparation of N-{[4-(1,3-dioxobenzo[c]azolidin-2-yl)phenyl]sulfonyl(phenylamino) carboxamide:

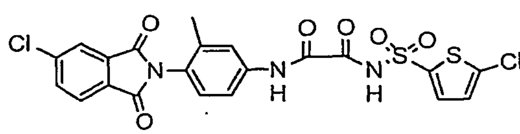
A. Synthesis of 4-(1,3-dioxobenzo[c]azolidin-2-yl)benzenesulfonamide

A solution of 1.0 g (5.8 mmol) of p-aminophenylsulfonamide in 3.6 mL of pyridine was added 878 μL (6.1 mmol) of phthalic dichoride. After heating to 60 °C for 18 h, the solution was poured into 1N HCl, cooled to 0 °C, the precipitate was collected by filtration, and dried under vacuum to give 1.58 g (90%) of the titled compound.

A. Synthesis of N-{[4-(1,3-dioxobenzo[c]azolidin-2-yl)phenyl]sulfonyl} (phenylamino)carboxamide

To a solution of 4-(1,3-dioxobenzo[c]azolidin-2-yl)benzenesulfonamide in 660 uL of DMSO was added 60 mg (0.40 mmol) of DBU followed by 36 μl (0.33 mmol) of phenylsulfonylisocyanate. After stirring for 0.5 h, the mixture was poured into 1N HCl, cooled, and the precipitate was collected by filtration and dried under vacuum to give 137 mg (100%) of the titled compound.

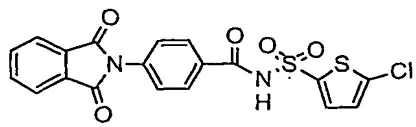
Example 1078



Preparation of N-[(5-chloro(2-thienyl))sulfonyl]-N'-[4-(5-chloro-1,3-dioxobenzo [c]azolidin-2-yl)-3-methylphenyl]ethane-1,2-diamide:

A 200 mg (1.0 mmol) of 5-chlorothiophenesulfonamide was slurried in 0.5 mL of oxalyl chloride and refluxed for 6h. The solvent was removed in vacuo and 36 mg of the resulting solid was dissolved in 240 μL acetonitrile and treated with 40 mg(0.14 mmol) 2-(4-amino-2-methylphenyl)-5-chlorobenzo[c]azoline-1,3-dione. After stirring for 1h, the solvent was removed and the residue was purified by RP-HPLC to give 33 mg (44%) of the titled compound. ES-MS (M+H)+= 538(2Cl).

Example 1079



Preparation of [4-(1,3-dioxobenzo[c]azolidin-2-yl)phenyl]-N-[(5-chloro(2-thienyl))sulfonyl]-carboxamide

A. Synthesis of N-[(5-chloro(2-thienyl))sulfonyl](4-nitrophenyl)carboxamide

A 85 mg portion (0.43 mmol) of 5- chlorothiophenesulfonamide dissolved in 2 mL of acetone was treated with 110 μL of 4N NaOH (0.43 mmol) followed by addition of 80 mg (0.43 mmol) of 4-nitrobenzoyl chloride. After stirring for 12 h, the solution was acidfied 1N HCl and the precipitate was collected by filtration and dried. Recrystallization from EtOAc/hexane afforded 120 mg (81%) of the titled compound. ES-MS (M+H)+ = 347 (Cl).

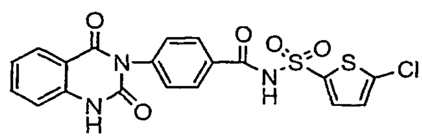
B. Synthesis of (4-aminophenyl)-N-[(5-chloro(2-thienyl))sulfonyl]carboxamide

A 74 mg portion (0.21 mmol) of [4-(1,3-dioxobenzo[c]azolidin-2-yl)phenyl]-N-[(5-chloro(2-thienyl))sulfonyl]-carboxamide, 192 mg (0.84 mmol) of tin dichloride dihydrate were combined and dissolved in 1.4 mL of EtOAc. The mixture was refluxed for 4h, filtered through celite, and concentrated in vacuo to afford a solid which was purified on silica gel eluting with 10% MeOH/CH_2Cl_2 to give a quantitative yield of the titled compound. ES-MS (M+H)+ = 317 (Cl).

C. Synthesis of [4-(1,3-dioxobenzo[c]azolidin-2-yl)phenyl]-N-[(5-chloro(2-thienyl))sulfonyl]carboxamide

A 22 mg portion (0.070) of (4-aminophenyl)-N-[(5-chloro(2-thienyl))sulfonyl]carboxamide was combined with 15 mg (0.10 mmol) of phthalic anhydride in 140 μL of DMF. After 18 h of heating at 110 °C, the mixture was cooled and purified by RP-HPLC, to give 20 mg (55%) of the desired compound. ES-MS $(M+H)^+ = 447$ (Cl).

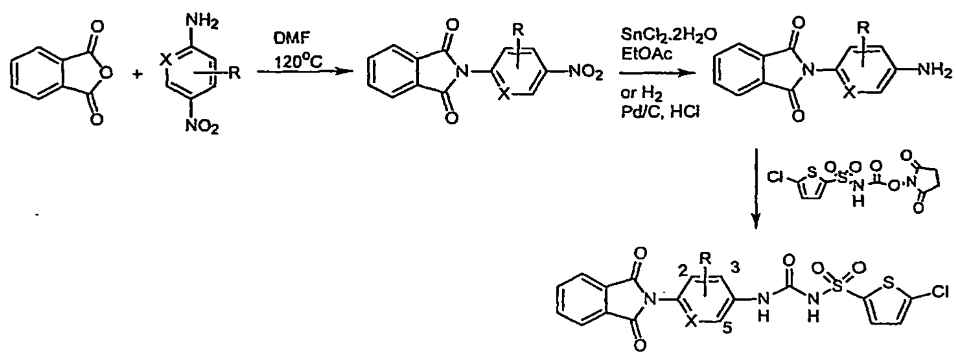
Example 1080



[4-(2,4-dioxo(1,3-dihydroquinazolin-3-yl))phenyl]-N-[(5-chloro(2-thienyl)) sulfonyl]carboxamide

A 44 mg portion (0.14) of (4-aminophenyl)-N-[(5-chloro(2-thienyl))sulfonyl]carboxamide was combined with 25 mg (0.14 mmol) of methyl 2-isocyanatobenzoate in 500 uL of THF followed by the addition of 1 equivalent of TEA (24 μL) and 1 equivalent of DBU. After 18h, the mixture was purified by RP-HPLC, to give 21 mg (34%) of the desired compound. ES-MS $(M+H)^+ = 462$ (Cl).

Scheme 1 General Synthesis of Phthalimide Compounds:



General Procedure for synthesizing phthalimide targets

A. General Procedure for phthalic anhydride reaction

A mixture of phthalic anhydride (0.96 g, 6.5 mmol) and the substituted nitroaniline (5 mmol) in DMF (10 mL) was heated to 120 °C for 22 hr. The reaction was then concentrated and chromatographed on silica gel using CH_2Cl_2/hexane mixtures as eluent to give pure product in 35-65% yields, depending on the substituents.

B-1. General reduction procedure 1

A suspension of the nitrophenyl intermediate (0.75 mmol) and tin(II) chloride dihydrate (3 mmol) in ethyl acetate (4.5 mL) was heated at 70°C for 2 hr. The reaction mixture was then poured onto ice (25 mL), basified with 5% $NaHCO_3$ (13 mL), extracted with EtOAc, washed with brine, dried and concentrated in vacuo to give pure aniline product in very good yields, typically >90%.

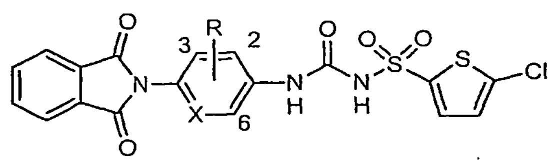
B-2. General reduction procedure 2

To a suspension of the nitrophenyl intermediate (0.8 mmol) in methanol (3 mL), ethyl acetate (2 mL) and 2 N HCl (0.4 mL, 0.8 mmol) was added 10% Pd/C (43 mg, 0.04 mmol) under argon. The reaction mixture was hydrogenated under 1 atm H_2 for 2 hr, filtered through Celite and concentrated in vacuo to give the aniline hydrochloride salt in very good yields.

C. General Procedure for coupling the aniline intermediate with 5-chlorothiophenesulfonamides to form sulfonyl ureas

To a suspension of 5-chlorothiophene-2-sulfonamide (40 mg, 0.2 mmol) and DSC (61 mg, 0.24 mmol) in dry acetonitrile (1 mL) was added DBU (60 μL, 0.4 mmol). The resulting solution was stirred at room temp for 16 hr. The aniline from step B (0.2 mmol) was then added as a solid with additional acetonitrile (1 mL), and the reaction was heated to 70°C and stirred for another 17 hr. Acidification and HPLC purification of the crude reaction product gave the final compounds in varying yields (20-70%).

Example 7 and Examples 1081-1093



The targets above were prepared using the procedures outlined in Scheme 1, steps A-C using a variety of substituted nitroanilines, where R = 3-Cl; 3-CN; 3-CF_3; 3-F; 3-Br; 3-OMe; 3-iPr; 2-CF_3; 2-Cl, 5-Me; 2-NMe_2, 5-Cl; 2,5-diMe; 3,5-diMe; 3,5-diCl; 2-OMe, 5-Me; and X = N, R = H.

Example 7

N-[4-(1,3-dioxobenzo[c]azolidin-2-yl)-3-chlorophenyl]{[(5-chloro(2-thienyl))sulfonyl]amino}-carboxamide. ES-MS (M+H)+ = 496, 498 (2Cl).

Example 1081

N-[4-(1,3-dioxobenzo[c]azolidin-2-yl)-3-cyanophenyl]{[(5-chloro(2-thienyl))sulfonyl]amino}-carboxamide. ES-MS (M+H)+ = 487, 489 (Cl).

Example 1082

N-[4-(1,3-dioxobenzo[c]azolidin-2-yl)-3-(trifluoromethyl) phenyl]{[(5-chloro(2-thienyl))sulfonyl]-amino}carboxamide. ES-MS (M+H)+ = 530, 532 (Cl).

Example 1083

N-[4-(1,3-dioxobenzo[c]azolidin-2-yl)-3-fluorophenyl]{[(5-chloro(2-thienyl))sulfonyl]amino}-carboxamide. ES-MS (M+H)+ = 530, 532 (Cl).

Example 1084

N-[4-(1,3-dioxobenzo[c]azolidin-2-yl)-3-bromophenyl]{[(5-chloro(2-thienyl))sulfonyl]amino}-carboxamide. ES-MS (M+H)+ = 540, 542 (Cl, Br).

Example 1085

N-[4-(1,3-dioxobenzo[c]azolidin-2-yl)-3-methoxyphenyl]{[(5-chloro(2-thienyl))sulfonyl]amino}-carboxamide. ES-MS (M+H)+ = 492.0 (Cl).

Example 1086

N-[4-(1,3-dioxobenzo[c]azolidin-2-yl)-3-(methylethyl)phenyl]{[(5-chloro(2-thienyl))sulfonyl]amino}-carboxamide. ES-MS (M+H)+ = 490.9 (Cl).

Example 1087

N-[4-(1,3-dioxobenzo[c]azolidin-2-yl)-2-(trifluoromethyl) phenyl]{[(5-chloro(2-thienyl))sulfonyl]-amino}carboxamide. ES-MS (M+H)+ = 463, 465 (Cl).

Example 1088

N-[4-(1,3-dioxobenzo[c]azolidin-2-yl)-2-chloro-5-methylphenyl]{[(5-chloro(2-thienyl))sulfonyl]-amino}carboxamide. ES-MS (M+H)+ = 510, 512 (2Cl).

Example 1089

N-[2-(dimethylamino)-4-(1,3-dioxobenzo[c]azolidin-2-yl)-5-chlorophenyl]{[(5-chloro(2-thienyl))-sulfonyl]amino}carboxamide. ES-MS (M+H)+ = 539, 541 (2Cl).

Example 1090

N-[4-(1,3-dioxobenzo[c]azolidin-2-yl)-2,5-dimethylphenyl]{[(5-chloro(2-thienyl))sulfonyl]amino}-carboxamide. ES-MS (M+H)+ = 490.0 (Cl).

Example 1091

N-[4-(1,3-dioxobenzo[c]azolidin-2-yl)-3,5-dimethylphenyl]{[(5-chloro(2-thienyl))sulfonyl]amino}-carboxamide. ES-MS (M+H)+ = 490.0 (Cl).

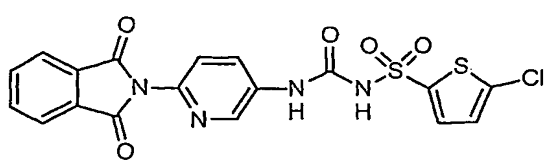
Example 1092

N-[4-(1,3-dioxobenzo[c]azolidin-2-yl)-3,5-dichlorophenyl]{[(5-chloro(2-thienyl))sulfonyl]amino}-carboxamide. ES-MS (M+H)+ = 529.9, 532.0 (2Cl)

Example 1093

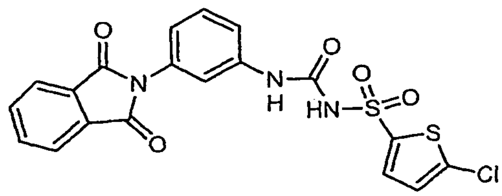
N-[4-(1,3-dioxobenzo[c]azolidin-2-yl)-5-methyl-2-methoxyphenyl]{[(5-chloro(2-thienyl))sulfonyl]-amino}carboxamide. ES-MS (M+H)+ = 506, 507 (Cl).

Example 1094



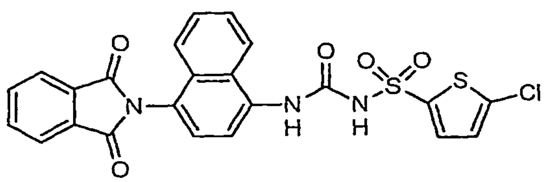
Preparation of N-[6-(1,3-dioxobenzo[c]azolidin-2-yl)(3-pyridyl)]{[(5-chloro(2-thienyl))sulfonyl]-amino}carboxamide was accomplished using the procedures outlined in Scheme 1, steps A-C using 2-amino-5-nitropyridine. ES-MS (M+H)+ = 463, 465 (Cl).

Example 1095



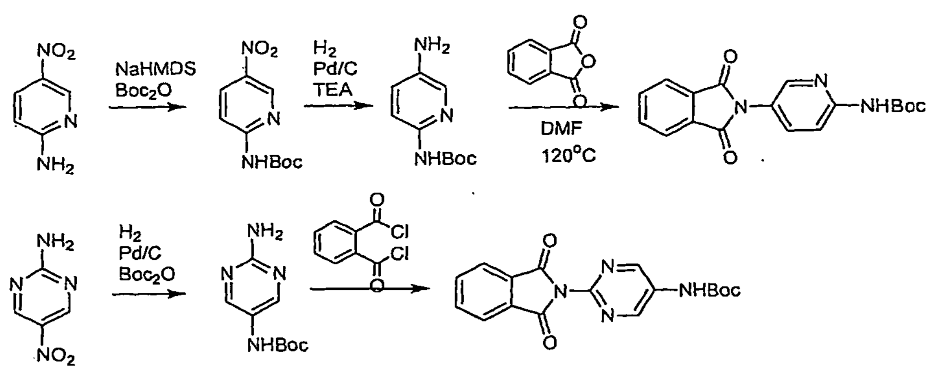
Preparation of N-[6-(1,3-dioxobenzo[c]azolidin-2-yl)(3-phenyl)]{[(5-chloro(2-thienyl))sulfonyl]-amino}carboxamide was accomplished using the procedures outlined in Scheme 1, steps A-C. ES-MS (M+H)+ = 462.0 (Cl).

Example 1096

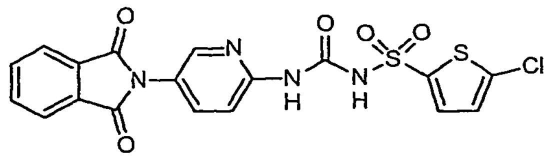


Preparation of N-[4-(1,3-dioxobenzo[c]azolidin-2-yl)-4-napthyl]{[(5-chloro(2-thienyl))sulfonyl]-amino}carboxamide was accomplished using the procedures outlined in Scheme 1, steps A-C. ES-MS (M+H)+ = 511.9 (Cl).

Scheme 2



Example 1097



Preparation of N-[5-(1,3-dioxobenzo[c]azolidin-2-yl)(2-pyridyl)]{[(5-chloro(2-thienyl))-sulfonyl]amino}carboxamide

A. Synthesis of (tert-butoxy)-N-(5-nitro(2-pyridyl))carboxamide

To a solution of 2-amino-5-nitropyridine (0.555 g, 4 mmol) in THF (10 mL) was added 1 M NaHMDS in THF (8 mL, 8 mmol). The resulting dark red suspension was stirred for 15 min, followed by addition of a solution of Boc anhydride (0.87 mL, 3.8 mmol) in THF (5 mL). The reaction mixture was stirred at room temp for 21 hr, dilute with EtOAc, washed with 1 N HCl and brine, dried and concentrated in vacuo to give (tert-butoxy)-N-(5-nitro(2-pyridyl))carboxamide (0.63 g, 70%). ES-MS (M+H-tBu)+ = 184.

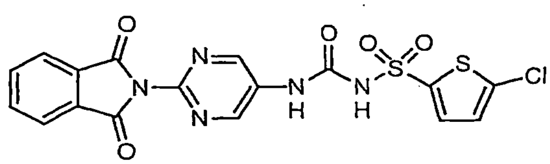
B. Synthesis of N-(5-amino(2-pyridyl))(tert-butoxy)carboxamide

To a suspension of (tert-butoxy)-N-(5-nitro(2-pyridyl))carboxamide (0.27 g, 1.13 mmol) in methanol (2 mL), ethyl acetate (4 mL) and TEA (0.16 mL) was added 10% Pd/C (60 mg, 0.056 mmol) under argon. The reaction mixture was hydrogenated under 1 atm H_2 for 20 hr, filtered through Celite and concentrated in vacuo to give N-(5-amino(2-pyridyl))(tert-butoxy)carboxamide (0.226 g, 97%). ^{1}H-NMR (DMSO-d_6): δ 1.40 (s, 9H), 4.92 (br s, 2H), 6.89-6.91 (dd, 1H), 7.35-7.37 (d, 1H), 7.58 (d, 1H), 9.06 (s, 1H).

C. Synthesis of N-[5-(1,3-dioxobenzo[c]azolidin-2-yl)(2-pyridyl)]{[(5-chloro(2-thienyl))-sulfonyl]amino}carboxamide

N-[5-(1,3-dioxobenzo[c]azolidin-2-yl)(2-pyridyl)]{[(5-chloro(2-thienyl))-sulfonyl]amino}carboxamide was prepared by following the procedure in Scheme 1 step A, followed by TFA deprotection, followed by the coupling procedure outlines in Scheme 1 step C. ES-MS (M+H)+ = 463, 465 (Cl).

Example 1098



Preparation of N-[2-(1,3-dioxobenzo[c]azolidin-2-yl)pyrimidin-5-yl]{[(5-chloro(2-thienyl))sulfonyl]amino}carboxamide.

A. Synthesis of N-(2-aminopyrimidin-5-yl)(tert-butoxy)carboxamide

To a suspension of 2-amino-5-nitropyrimidine (0.25 g, 1.78 mmol) in methanol (4 mL) was added tert-butyl (tert-butoxycarbonyloxy)formate (0.5 mL, 2.18 mmol) and 10% Pd/C (96 mg, 0.090 mmol) under argon. The reaction mixture was hydrogenated under 1 atm H_2 for 5 hr, filtered through Celite and concentrated in vacuo to give crude N-(2-aminopyrimidin-5-yl)(tert-butoxy)carboxamide (0.435 g). ES-MS (M+H)+ = 211.

B. Synthesis of (tert-butoxy)-N-[2-(1,3-dioxobenzo[c]azolidin-2-yl)pyrimidin-5-yl]carboxamide

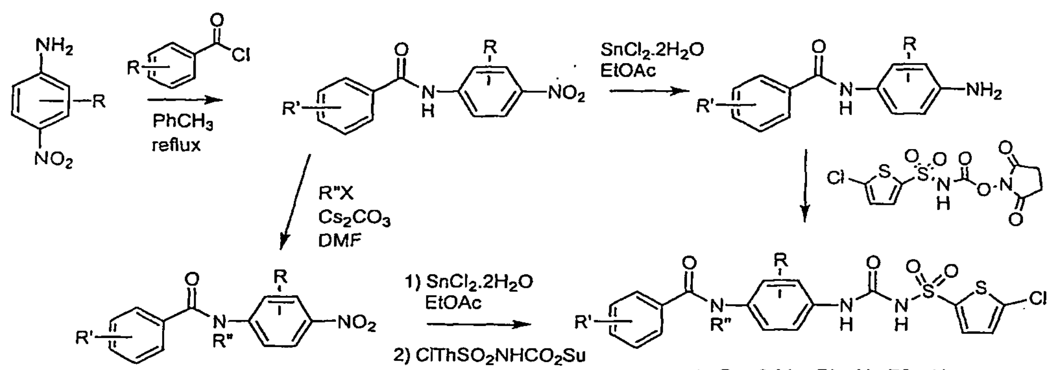
To a solution of N-(2-aminopyrimidin-5-yl)(tert-butoxy)carboxamide (0.237 g, 1.0 mmol) in pyridine (1 mL) was added phthaloyl dichloride (0.144 mL, 1.0 mmol). The resulting suspension was stirred at 45 °C for 2 hr, diluted with EtOAc, washed with water and brine, dried and concentrated in vacuo to give crude (tert-butoxy)-N-[2-(1,3-

dioxobenzo[c]azolidin-2-yl)pyrimidin-5-yl]carboxamide (0.31 g). ES-MS (M+H)+ = 341; (M+H-tBu)+ = 285.

C. Synthesis of N-[2-(1,3-dioxobenzo[c]azolidin-2-yl)pyrimidin-5-yl]{[(5-chloro(2-thienyl))sulfonyl]amino}carboxamide

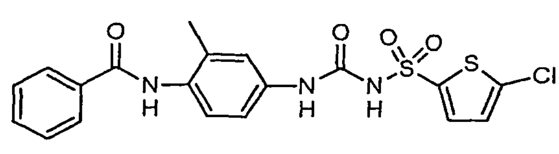
TFA deprotection of (tert-butoxy)-N-[2-(1,3-dioxobenzo[c]azolidin-2-yl)pyrimidin-5-yl]carboxamide and coupling with 5-chlorothiophenesulfonamide (see Scheme 1 step C) gave N-[2-(1,3-dioxobenzo[c]azolidin-2-yl)pyrimidin-5-yl]{[(5-chloro(2-thienyl))sulfonyl]amino}carboxamide in 27% yield. ES-MS (M+H)+ = 464, 466 (Cl).

Scheme 3 Benzamide-containg Sulfonylureas



1: R = 2-Me, R' = H, R" = H
2: R = 2-Me, R' = H, R" = Me
3: R = 2-Me, R' = Cl, R" = H
4: R = 2-Br, R' = H, R" = H

Example 1099



Preparation of N-[4-({[(5-chloro(2-thienyl))sulfonyl]amino}carbonylamino)-2-methylphenyl]-benzamide

A. Synthesis of N-(2-methyl-4-nitrophenyl)benzamide

To a suspension of 2-methyl-4-nitroaniline (0.76 g, 5 mmol) in toluene (25 mL) was added neat benzoyl chloride (0.59 mL, 5.08 mmol). The reaction mixture was refluxed for 16 hr, cooled and filtered to give N-(2-methyl-4-nitrophenyl)benzamide (1.21 g, 95%) as a beige solid. ES-MS (M+H)+ = 257.

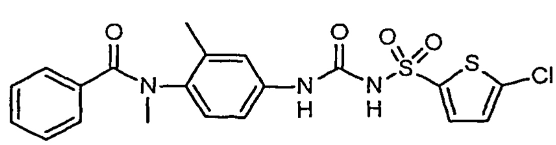
B. Synthesis of N-(4-amino-2-methylphenyl)benzamide

A suspension of N-(2-methyl-4-nitrophenyl)benzamide (0.256 g, 1.0 mmol) and tin(II) chloride dihydrate (0.89 g, 3.96 mmol) in ethyl acetate (6 mL) was heated at 70 °C for 19 hr. The reaction mixture was then chilled, poured onto 50 mL ice, basified with 5% $NaHCO_3$ (20 mL), extracted into EtOAc, washed with brine, dried and concentrated in vacuo to give N-(4-amino-2-methylphenyl)-benzamide (0.22 g, 97%). ES-MS (M+H)+ = 227, (M+Na)+ = 249.

C. Synthesis of N-[4-({[(5-chloro(2-thienyl))sulfonyl]amino}carbonylamino)-2-methylphenyl]benzamide

A solution of 5-chlorothiophene-2-sulfonamide (30 mg, 0.15 mmol) and DSC (46 mg, 0.18 mmol) in CH_3CN (1 mL) and DBU (45 μL) was heated at 40°C for 1 hr. To this mixture was added N-(4-amino-2-methylphenyl)benzamide (34 mg, 0.15 mmol) with further heating for 3 days. Acidification and HPLC purification gave N-[4-({[(5-chloro(2-thienyl))sulfonyl]amino}carbonyl-amino)-2-methylphenyl]benzamide (24 mg, 35%). ES-MS (M+H)+ = 450, 452 (Cl).

Example 1100



Preparation of N-[4-({[(5-chloro(2-thienyl))sulfonyl]amino}carbonylamino)-2-methylphenyl]-N-methylbenzamide

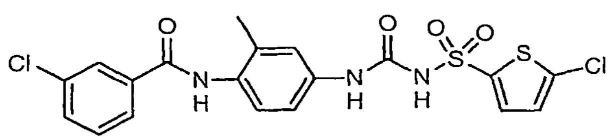
A. Synthesis of N-methyl-N-(2-methyl-4-nitrophenyl)benzamide

To a solution of N-(2-methyl-4-nitrophenyl)benzamide (Example 1099A) (0.38 g, 1.48 mmol) in DMF (2 mL) was added cesium carbonate (1.2 g, 3.68 mmol) followed by methyl iodide (0.12 mL, 1.9 mmol). The reaction mixture was stirred at room temp for 2 hr, extracted with EtOAc, washed with water and brine, dried and concentrated in vacuo to give N-methyl-N-(2-methyl-4-nitrophenyl)-benzamide (0.38 g, 95%). ES-MS (M+H)+ = 271.

B. Synthesis of N-[4-({[(5-chloro(2-thienyl))sulfonyl]amino}carbonylamino)-2-methylphenyl]-N-methylbenzamide

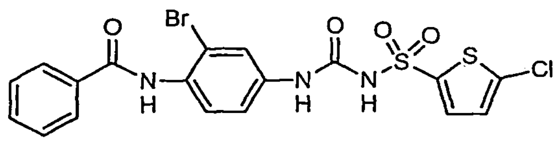
N-methyl-N-(2-methyl-4-nitrophenyl)benzamide was reduced and coupled with 5-chloro-thiophenesulfonamide using the same procedure as shown in Example 1099, steps B and C to give N-[4-({[(5-chloro(2-thienyl))sulfonyl] amino}carbonylamino)-2-methylphenyl]-N-methylbenzamide (44 mg, 31%). ES-MS (M+H)+ = 464, 466 (Cl).

Example 1101



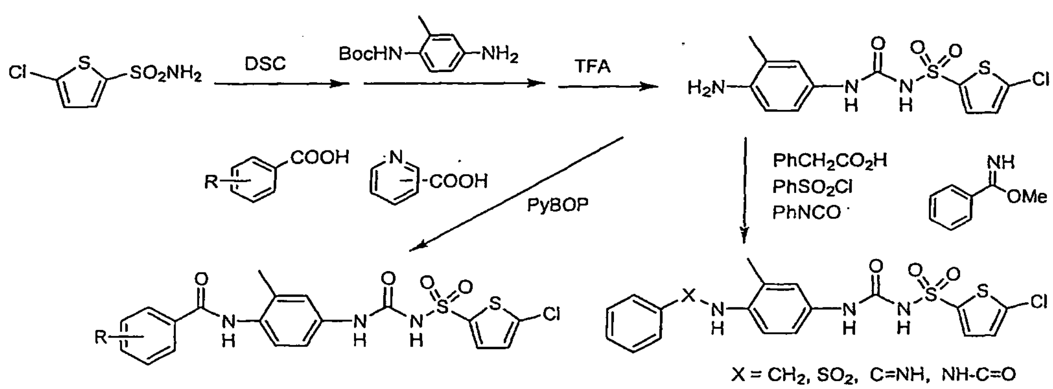
Preparation of N-[4-({[(5-chloro(2-thienyl))sulfonyl]amino}carbonylamino)-2-methylphenyl](3-chlorophenyl)-carboxamide was prepared using a similar procedure as that shown in Example 1099 steps A-C, using 3-chlorobenzoyl chloride in the first step, instead of benzoyl chloride. The final product was obtained in 43% yield. ES-MS (M+H)+ = 484, 486 (2Cl).

Example 1102

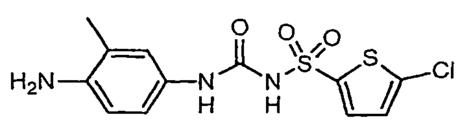


Preparation of N-[2-bromo-4-({[(5-chloro(2-thienyl))sulfonyl]amino}carbonylamino)phenyl] benzamide was prepared using a similar procedure as that shown in Example 1099 steps A-C, using 2-bromo-4-nitro-aniline in the first step, instead of 2-methyl-4-nitroaniline. The final product was obtained in 64% yield. ES-MS (M+H)+ = 514, 516, 518 (Cl, Br).

Scheme 4



Example 1103



Preparation of N-(4-amino-3-methylphenyl){[(5-chloro(2-thienyl))sulfonyl] amino}carboxamide

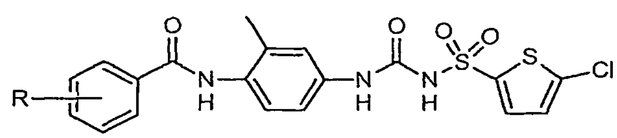
A. Synthesis of N-{4-[(tert-butoxy)carbonylamino]-3-methylphenyl}{[(5-chloro(2-thienyl))sulfonyl]amino}carboxamide

A solution of 5-chlorothiophene-2-sulfonamide (0.2 g, 1.0 mmol) and DSC (0.307 g, 1.2 mmol) in CH_2Cl_2 (5 mL) and DBU (0.3 mL) was stirred at room temp for 16 hr. To this mixture was added N-(4-amino-2-methylphenyl)(tert-butoxy)carboxamide (0.26 g, 1 mmol), followed by heating at 40 °C for 2hr. Acidification and HPLC purification gave N-{4-[(tert-butoxy)carbonylamino]-3-methyl-phenyl} {[(5-chloro(2-thienyl))sulfonyl]amino}carboxamide (0.28 g, 63%). ES-MS (M+Na)+ = 468, (M+H-tBu) = 390, 392 (Cl).

B. Synthesis of N-(4-amino-3-methylphenyl){[(5-chloro(2-thienyl))sulfonyl]amino}carboxamide

To a chilled solution of N-{4-[(tert-butoxy)carbonylamino]-3-methylphenyl} {[(5-chloro(2-thienyl))sulfonyl]amino}carboxamide (0.246 g, 0.55 mmol) in CH_2Cl_2 (5 mL) was added neat TFA (1.1 mL). The reaction mixture was stirred cold for 1.5 hr, concentrated in vacuo, azeotroped with heptane and dried to give N-(4-amino-3-methylphenyl){[(5-chloro(2-thienyl))sulfonyl]amino}-carboxamide (0.26 g) as the mono TFA salt. ES-MS (M+H)+ = 346.

Examples 1104-1116



The compounds above were prepared according to Scheme 4 using the following general synthetic procedure: 1.1 equivalent of the benzoic acid and 1 equivalent of N-(4-amino-3-methylphenyl){[(5-chloro(2-thienyl))sulfonyl]amino}carboxamide were dissolved in DMF (0.5 M) and 1.2 equivalent of PyBOP was added. After 2h, the reaction mixture was directly purified by RP-HPLC to give the targets above where R = p-CH_3, p-OCH_3, p-Cl, o-Cl, o-NO_2, o-OBn, o-OH, m-F, m,p-diCl, o-pyr, m-pyr and p-pyr. The o-NH_2 analog was obtained by reduction of o-NO_2 using H_2/Pt/C in methanol.

Example 1104

N-[4-({[(5-chloro(2-thienyl))sulfonyl]amino}carbonylamino)-2-methylphenyl](4-methylphenyl)-carboxamide. ES-MS (M+H)+ = 464, 466 (Cl).

Example 1105

N-[4-({[(5-chloro(2-thienyl))sulfonyl]amino}carbonylamino)-2-methylphenyl](4-methoxyphenyl)-carboxamide. ES-MS (M+H)+ = 480, 482 (Cl).

Example 1106

N-[4-({[(5-chloro(2-thienyl))sulfonyl]amino}carbonylamino)-2-methylphenyl](4-chlorophenyl)-carboxamide. ES-MS (M+H)+ = 483.9, 485.9, 487.9 (2Cl).

Example 1107

N-[4-({[(5-chloro(2-thienyl))sulfonyl]amino}carbonylamino)-2-methylphenyl](2-chlorophenyl)-carboxamide. ES-MS (M+H)+ = 484, 486 (2Cl).

Example 1108

N-[4-({[(5-chloro(2-thienyl))sulfonyl]amino}carbonylamino)-2-methylphenyl](2-nitrophenyl)-carboxamide. ES-MS (M+H)+ = 495, 497 (Cl).

Example 1109

N-[4-({[(5-chloro(2-thienyl))sulfonyl]amino}carbonylamino)-2-methylphenyl][2-(phenylmethoxy)-phenyl]carboxamide. ES-MS (M+H)+ = 556, 558 (Cl).

Example 1110

N-[4-({[(5-chloro(2-thienyl))sulfonyl]amino}carbonylamino)-2-methylphenyl][2-hydroxyphenyl]-carboxamide. ES-MS (M+H)+ = 466, 468 (Cl).

Example 1111

N-[4-({[(5-chloro(2-thienyl))sulfonyl]amino}carbonylamino)-2-methylphenyl](3-fluorophenyl)-carboxamide. ES-MS (M+H)+ = 468, 470 (Cl).

Example 1112

N-[4-({[(5-chloro(2-thienyl))sulfonyl]amino}carbonylamino)-2-methylphenyl](3,4-dichlorophenyl)-carboxamide. ES-MS (M+H)+ = 517.9, 519.9, 521.9 (3Cl).

Example 1113

N-[4-({[(5-chloro(2-thienyl))sulfonyl]amino}carbonylamino)-2-methylphenyl]-2-pyridylcarboxamide. ES-MS (M+H)+ = 451, 453 (Cl).

Example 1114

N-[4-({[(5-chloro(2-thienyl))sulfonyl]amino}carbonylamino)-2-methylphenyl]-3-pyridylcarboxamide. ES-MS (M+H)+ = 451, 453 (Cl).

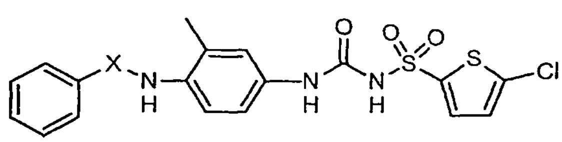
Example 1115

N-[4-({[(5-chloro(2-thienyl))sulfonyl]amino}carbonylamino)-2-methylphenyl]-4-pyridylcarboxamide. ES-MS (M+H)+ = 451, 453 (Cl).

Example 1116

N-[4-({[(5-chloro(2-thienyl))sulfonyl]amino}carbonylamino)-2-methylphenyl](2-aminophenyl)-carboxamide. ES-MS (M+H)+ = 465, 467 (Cl).

Example 1117-1120



Example 1117

1.0 equivalent of N-(4-amino-3-methylphenyl){[(5-chloro(2-thienyl))sulfonyl]amino}-carboxamide was treated with 1.0 equivalent of $PhCH_2COOH$/PyBOP to give X = CH_2, {[(5-chloro(2-thienyl))sulfonyl]amino}-N-{3-methyl-4-[benzylamino]phenyl}carboxamide. ES-MS (M+H)+ = 464, 466 (Cl).

Example 1118

Alternatively (for X=SO_2), the compounds above were prepared according to Scheme 4 using the following general synthetic procedure: 1.0 equivalents of N-(4-amino-3-methylphenyl){[(5-chloro(2-thienyl))sulfonyl]amino}-carboxamide dissolved in DMF (0.5 M) was treated with 1.0 equivalent of $PhSO_2Cl$ and 1.2 equivalents of DIEA to give, after RP-HPLC purification, X = SO_2, {[(5-chloro(2-thienyl))sulfonyl]amino}-N-{3-methyl-4-[(phenylsulfonyl)amino]phenyl}carboxamide. ES-MS (M+H)+ = 486, 488 (Cl).

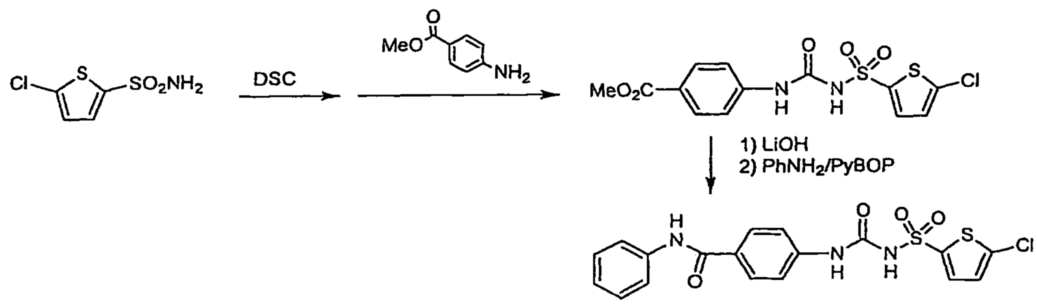
Example 1119

For X = C=NH: Treatment with methyl benzimidate.HCl (1.4 eq) in DMF gave the amidine X = C=NH, {[(5-chloro(2-thienyl))sulfonyl]amino}-N-{4-[(iminophenylmethyl)amino]-3-methylphenyl}carboxamide. ES-MS (M+H)+ = 449, 451 (Cl).

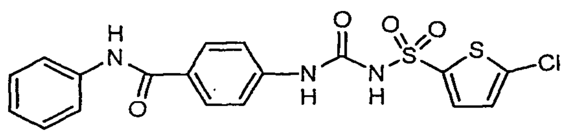
Example 1120

For X = NH-C=O: Treatment with phenyl isocyanate (1.07 eq) in DMF to give the urea X = NH-C=O, {[(5-chloro(2-thienyl))sulfonyl]amino}-N-{3-methyl-4-[(phenylamino)carbonylamino]phenyl} carboxamide. ES-MS (M+H)+ = 465, 467 (Cl).

Scheme 5



Example 1121



Preparation of {[(5-chloro(2-thienyl))sulfonyl]amino}-N-[4-(N-phenylcarbamoyl)phenyl] carboxamide

A. Synthesis of methyl 4-({[(5-chloro-2-thienyl)sulfonyl]amino}carbonylamino)benzoate

A solution of 5-chlorothiophene-2-sulfonamide (0.2 g, 1.0 mmol) and DSC (0.307 g, 1.2 mmol) in CH_2Cl_2 (5 mL) and DBU (0.3 mL) was stirred at room temp overnight. To this mixture was added methyl 4-aminobenzoate (0.15 g, 1.0 mmol). The reaction was then stirred at room temp for 17 hr, acidified and HPLC purified to give methyl 4-({[(5-chloro-2-thienyl)sulfonyl]amino}carbonyl-amino)benzoate (0.23 g, 61%). ES-MS $(M+H)+ = 375, 377$ (Cl).

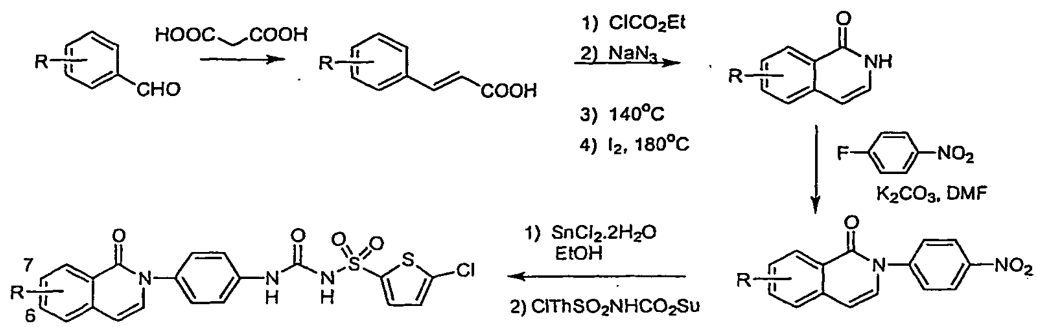
B. Synthesis of 4-({[(5-chloro-2-thienyl)sulfonyl]amino}carbonylamino)benzoic acid

To a suspension of methyl 4-({[(5-chloro-2-thienyl)sulfonyl]amino}carbonylamino)benzoate (56 mg, 0.15 mmol) in methanol (1 mL) and acetonitrile (1 mL) was added 1N LiOH (0.16 mL, 0.16 mmol). The resulting solution was stirred at room temp for 21 hr, then an additional 0.32 mL 1N LiOH was added and the reaction was stirred at 40 °C for another 21 hr til complete. Concentration in vacuo gave crude 4-({[(5-chloro-2-thienyl)sulfonyl]amino}carbonylamino)benzoic acid (69 mg). ES-MS (M+H)+ = 361.

C. Synthesis of {[(5-chloro(2-thienyl))sulfonyl]amino}-N-[4-(N-phenylcarbamoyl)phenyl]-carboxamide

To a solution of 4-({[(5-chloro-2-thienyl)sulfonyl]amino}carbonylamino)benzoic acid (69 mg) in DMF (0.7 mL) was added aniline (21 uL, 0.23 mmol), DIEA (3 eq.) then PyBOP (85 mg, 0.16 mmol). The reaction mixture was stirred at room temp for 28 hr, acidified and HPLC purified to give {[(5-chloro(2-thienyl))sulfonyl]amino}-N-[4-(N-phenylcarbamoyl)phenyl]carboxamide (29 mg, 45%). ES-MS (M+H)+ = 436, 438 (Cl).

Scheme 6: General Procedure for the Synthesis of Isoquinolinone –containing Sulfonylureas



R=	6,7-diCl	7-Me	6-Me, $-CF_3$, -Cl
	7,8-diCl	7-Cl	6-OMe, 6-OH, 6-OiPr, 6-OCH_2CH_2OMe
	7-Cl, 6-OMe	7-CF_3	6-NH_2, -NHAc, -NHMe, -NMe_2
		7-F	6-NHEt, -NHPr, -$NHCH_2cPr$, -NCH_2CH_2F, -NHBn
	8-NHMe	7-SMe	6-$NHCH_2CH_2OMe$
	8-CN	7-OMe	6-NHPh
		7-SOMe	6-F
	4-CO_2H	7-SO_2Me	6-$NHNH_2$
	4-$CONH_2$	7-CN	6-Br, -CN

General Procedure for synthesizing Isoquinolinone-containing Sulfonyl Ureas

A. General Procedure for synthesis of cinnamic acids

To a solution of malonic acid (10.4 g, 0.1 mol) and the benzaldehyde (0.05 mol) in pyridine (20 mL) was added neat piperidine (0.75 mL, 7.6 mmol). The reaction mixture was stirred at 80 °C for 17 hr, chilled, then added to 200 mL cold water. This mixture was acidified with conc. HCl (25 mL) and the white precipitate collected by filtration, washed with 5 x 10mL water, and dried to give pure cinnamic acid in typical yields of >95%.

B-1. General Procedure 1 for cyclization of cinnamic acids to isoquinolinones

To a chilled suspension of the cinnamic acid (25 mmol) in benzene (40 mL) and DMF (5 drops) was added neat thionyl chloride (2.2 mL, 30 mmol). The reaction mixture was stirred at 60 °C for 2 hr, chilled, concentrated in vacuo and dried to give crude acid chloride. To a solution of the acid chloride in 1,2-dichlorobenzene (22 mL) was added NaN_3 (2.6 g, 40 mmol). After heating at 140 °C for 6 hr, complete conversion to the isocyanate was observed, catalytic I_2 was added and the reaction was heated to 180 °C for 17 hr. Reaction workups included either precipitation of product with hexane or concentration and flash chromatography using $EtOAc/CH_2Cl_2$ eluent. Yields varied widely depending on the substituent (5-80%).

B-2. General Procedure 2 for cyclization of cinnamic acids to isoquinolinones

To a chilled solution of the cinnamic acid (16 mmol) in dry THF (35 mL) and triethylamine (2.9 mL, 20.8 mmol) was added neat ethyl chloroformate (1.85 mL, 19.4 mmol) dropwise over several minutes. The resulting suspension was stirred cold for 1 hr, then a solution of NaN_3 (1.56 g, 24 mmol) in 10 mL water was added. The reaction was stirred at room temp. for 1 hr. Reaction workups included either collection of the reaction precipitate, or extraction of product into CH_2Cl_2, giving pure acyl azide in >90% yields. A solution of the acyl azide in 1,2-dichlorobenzene (18 mL) was then heated to 140°C to form the isocyanate, followed by addition of cat. iodine and heating to 180 °C overnight. Workups were the same as in general procedure B-1.

C. General Procedure for alkylation of isoquinolinone with 1-fluoro-4-nitrobenzene

To a solution of the isoquinolinone (2.5 mmol) in DMF (5 mL) was added potassium carbonate (0.7 g, 5 mmol), followed by neat fluoro-4-nitrobenzene (0.3 mL, 2.8 mmol). The reaction mixture was stirred at 90 °C for 8 hr, poured onto cold water and filtered to give pure product in typical yields of 85-95%.

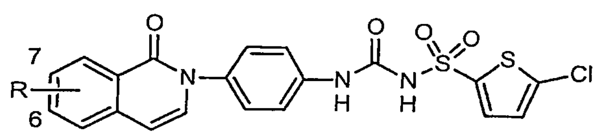
D. General reduction procedure

A suspension of the nitrophenyl intermediate from C (0.75 mmol) and tin(II) chloride dihydrate (0.68 g, 3 mmol) in ethanol (8 mL) was stirred at 70 °C for 4 hr. The reaction was then chilled, diluted with EtOAc, mixed with Celite, basified with 1M Na_2CO_3 (20 mL) then filtered. The organic layer was washed with water and brine, dried with Na_2SO_4, concentrated in vacuo to give the product aniline in typical yields of 85-95%.

E. General Procedure for coupling the aniline intermediate with 5-chlorothiophenesulfonamide

To a suspension of 5-chlorothiophene-2-sulfonamide (40 mg, 0.2 mmol) and DSC (61 mg, 0.24 mmol) in dry acetonitrile (1 mL) was added DBU (60 μL, 0.4 mmol). The resulting solution was stirred at room temp for 16 hr. The aniline from D (0.2 mmol) was then added as a solid with additional acetonitrile (1 mL), and the reaction was heated to 70 °C and stirred for another 17 hr. Acidification and HPLC purification of the crude reaction gave the final target in varying yields (20-70%) depending on the substituent.

Examples 371,372,374,376,379,380 and 1122-1128



The compounds above where , for example, R = 7-CH_3, 7-Cl, 7-F, 7-CF_3, 7-OCH_3, 6-CH3, 6-Cl, 6-F, 6-Br, 6-CF_3, 6-OCH_3, and 6,7-diCl were synthesized from commercially available benzaldehydes or cinnamic acids using the general procedure outlined in Scheme 6. The 7,8-diCl analog was isolated as a by-product during the synthesis of the 6,7-isomer.

Example 371

{[(5-chloro(2-thienyl))sulfonyl]amino}-N-[4-(6-methoxy-1-oxo(2-2-hydroisoquinolyl))-phenyl]carboxamide. ES-MS (M+H)+ = 490, 492 (Cl).

Example 372

{[(5-chloro(2-thienyl))sulfonyl]amino}-N-[4-(6-chloro-1-oxo(2-2-hydroisoquinolyl))-phenyl]carboxamide. ES-MS (M+H)+ = 494, 496, 498 (2Cl).

Example 374

{[(5-chloro(2-thienyl))sulfonyl]amino}-N-[4-(7-chloro-1-oxo(2-2-hydroisoquinolyl))phenyl]-carboxamide. ES-MS (M+H)+ = 494, 496, 498 (2Cl).

Example 376

{[(5-chloro(2-thienyl))sulfonyl]amino}-N-[4-(7-fluoro-1-oxo(2-2-hydroisoquinolyl))phenyl]-carboxamide. ES-MS (M+H)+ = 478.0 (Cl).

Example 379

{[(5-chloro(2-thienyl))sulfonyl]amino}-N-[4-(7-trifluoromethyl-1-oxo(2-2-hydroisoquinolyl))-phenyl]carboxamide. ES-MS (M+H)+ = 528, 530 (Cl).

Example 380

{[(5-chloro(2-thienyl))sulfonyl]amino}-N-[4-(7-methoxy-1-oxo(2-2-hydroisoquinolyl))-phenyl]carboxamide. ES-MS (M+H)+ = 490, 492 (Cl).

Example 1122

{[(5-chloro(2-thienyl))sulfonyl]amino}-N-[4-(7-methyl-1-oxo(2-2-hydroisoquinolyl))phenyl]-carboxamide. ES-MS (M+H)+ = 473.9, 475.9 (Cl).

Example 1123

{[(5-chloro(2-thienyl))sulfonyl]amino}-N-[4-(6-methyl-1-oxo(2-2-hydroisoquinolyl))-phenyl]carboxamide. ES-MS (M+H)+ = 474, 476 (Cl).

Example 1124

{[(5-chloro(2-thienyl))sulfonyl]amino}-N-[4-(6-fluoro-1-oxo(2-2-hydroisoquinolyl))-phenyl]carboxamide. ES-MS (M+H)+ = 477.9 (Cl).

Example 1125

{[(5-chloro(2-thienyl))sulfonyl]amino}-N-[4-(6-bromo-1-oxo(2-2-hydroisoquinolyl))-phenyl]carboxamide. ES-MS (M+H)+ = 537.9 (Cl).

Example 1126

{[(5-chloro(2-thienyl))sulfonyl]amino}-N-[4-(6-trifluoromethyl-1-oxo(2-2-hydroisoquinolyl))-phenyl]carboxamide. ES-MS (M+H)+ = 528, 530 (Cl).

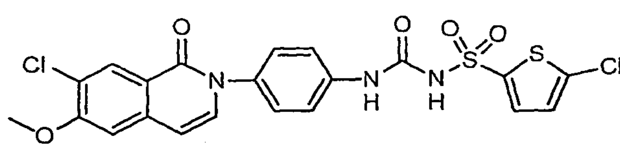
Example 1127

N-[4-(6,7-dichloro-1-oxo(2-2-hydroisoquinolyl))phenyl]{[(5-chloro(2-thienyl))sulfonyl]-amino}carboxamide. ES-MS (M+H)+ = 528, 530, 532 (3Cl).

Example 1128

N-[4-(7,8-dichloro-1-oxo(2-2-hydroisoquinolyl))phenyl]{[(5-chloro(2-thienyl))sulfonyl]-amino}carboxamide. ES-MS (M+H)+ = 528, 530, 532 (3Cl).

Example 1129



Preparation of {[(5-chloro(2-thienyl))sulfonyl]amino}-N-[4-(7-chloro-6-methoxy-1-oxo(2-2-hydroisoquinolyl))phenyl]carboxamide

A. Synthesis of 4-chloro-3-methoxytoluene

To a solution of 2-chloro-5-methylphenol (10.7 g, 75 mmol) in DMF (40 mL) was added potassium carbonate (26 g, 188 mmol) followed by neat methyl iodide (4.9 mL, 79 mmol). The reaction mixture was stirred at room temp for 6 hr, extracted with EtOAc, washed with water and brine, dried and concentrated in vacuo to give 4-chloro-3-methoxytoluene (10.8 g, 92%). ^{1}H-NMR (DMSO-d_6): δ 2.26 (s, 3H), 3.79 (s, 3H), 6.71-6.73 (dd, 1H), 6.94 (s, 1H), 7.22-7.24 (d, 1H).

B. Synthesis of 4-chloro-3-methoxybenzoic acid

To the crude toluene (7.8 g, 50 mmol) was added a solution $KMnO_4$ (19.8 g, 125 mmol) in water (300 mL). The reaction mixture was stirred vigorously at reflux for 17 hr and filtered warm through Celite, washing the cake with 200 mL hot water. The clear filtrate was washed with ethyl ether (2 x 150 mL), acidified with conc. HCl (9 mL) and filtered to give pure white solid 4-chloro-3-methoxybenzoic acid (5.36 g, 58%). ES-MS (M+H)+ = 187.

C. Synthesis of (4-chloro-3-methoxyphenyl)methan-1-ol

To a solution of 4-chloro-3-methoxybenzoic acid (4.88 g, 26.2 mmol) in THF (50 mL) was added borane-THF complex (52 mL 1M solution in THF, 52 mmol) via addition funnel over 10 min. The reaction mixture was refluxed for 2 hr, cooled, extracted with EtOAc, washed with water, 5% Na_2CO_3 and brine, dried and concentrated in vacuo to give (4-chloro-3-methoxyphenyl)methan-1-ol (4.5 g, 99%). ES-MS (M+H-H_2O)+ = 155, 157 (Cl).

D. Synthesis of 4-chloro-3-methoxybenzaldehyde

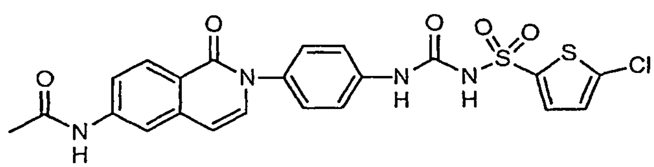
To a solution of (4-chloro-3-methoxyphenyl)methan-1-ol (5.08 g, 29.4 mmol) in benzene (120 mL) was added MnO_2 (5.65 g, 65 mmol). The reaction mixture was

refluxed for 17 hr, chilled, and filtered through Celite, washing the cake with CH_2Cl_2 (300 mL). The filtrate was concentrated in vacuo to give 4-chloro-3-methoxybenzaldehyde (4.5 g, 89%).

E. Synthesis of {[(5-chloro(2-thienyl))sulfonyl]amino}-N-[4-(7-chloro-6-methoxy-1-oxo(2-2-hydroisoquinolyl))phenyl]carboxamide

{[(5-chloro(2-thienyl))sulfonyl]amino}-N-[4-(7-chloro-6-methoxy-1-oxo(2-2-hydroisoquinolyl))phenyl]carboxamide was synthesized from the benzaldehyde using the general procedure outlined in Scheme 6, steps A-E. ES-MS (M+H)+ = 489, 491 (Cl).

Example 1130



Preparation of N-{2-[4-({[(5-chloro(2-thienyl))sulfonyl]amino}carbonylamino) phenyl]-1-oxo-6-2-hydroisoquinolyl}acetamide

A. Synthesis of N-(3-formylphenyl)acetamide

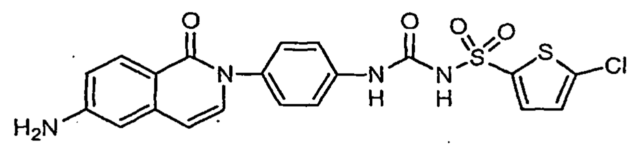
To a chilled suspension of 3-aminobenzyl alcohol (9.24 g, 75 mmol) in THF (50 mL) was added neat acetic anhydride (8.1 mL, 86 mmol). The reaction mixture was stirred cold for 1 hr, diluted with EtOAc, washed with aq. NaOH and brine, and concentrated in vacuo to give N-[3-(hydroxymethyl)phenyl]acetamide (10.5 g, 85%).

A mixture of N-[3-(hydroxymethyl)phenyl]acetamide (10 g, 60.6 mmol) and MnO_2 (7.8 g, 90 mmol) in toluene (250 mL) was refluxed for 29 hr, with addition of more MnO_2 (0.7 g, 9 mmol) at 24 hr. The reaction was cooled, filtered through Celite and concentrated in vacuo to give N-(3-formylphenyl)acetamide (9.2 g, 75%). ES-MS (M+H)+ = 164.

B. Synthesis of N-{2-[4-({[(5-chloro(2-thienyl))sulfonyl]amino} carbonylamino)phenyl]-1-oxo-6-2-hydroisoquinolyl}acetamide

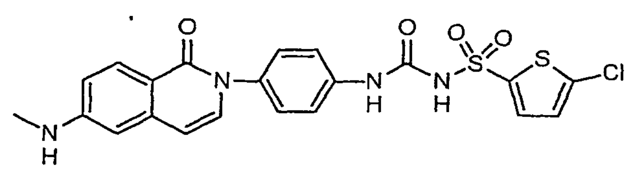
N-{2-[4-({[(5-chloro(2-thienyl))sulfonyl]amino}carbonylamino)phenyl]-1-oxo-6-2-hydroisoquinolyl}acetamide was synthesized from N-(3-formylphenyl)acetamide using the general procedure outlined in Scheme 6, steps A-E. ES-MS (M+H)+ = 517, 519 (Cl).

Example 1131



Preparation of N-[4-(6-amino-1-oxo(2-2-hydroisoquinolyl))phenyl]{[(5-chloro(2-thienyl))sulfonyl]amino}-carboxamide: This compound was synthesized by treating N-{2-[4-({[(5-chloro(2-thienyl))sulfonyl]amino}carbonyl-amino)phenyl]-1-oxo-6-2-hydroisoquinolyl}acetamide with 30 equiv. NaOMe in MeOH and refluxing overnight. It was also synthesized by treatment with neat hydrazine hydrate at 70 °C. ES-MS (M+H)+ = 475, 477 (Cl).

Example 373



Preparation of {[(5-chloro(2-thienyl))sulfonyl]amino}-N-{4-[6-(methylamino)-1-oxo(2-2-hydroisoquinolyl)]phenyl}carboxamide

A. Synthesis of N-methyl-N-[2-(4-nitrophenyl)-1-oxo(6-2-hydroisoquinolyl)]acetamide

To a solution of crude N-[2-(4-nitrophenyl)-1-oxo-6-2-hydroisoquinolyl]acetamide (0.26 g, 0.8 mmol) in DMF (2 mL) was added cesium carbonate (0.645 g, 2 mmol) followed by neat methyl iodide (75 μL, 1.2 mmol). The reaction mixture was stirred at room temp for 17 hr, precipitated with addition of water and filtered to give N-methyl-N-[2-(4-nitrophenyl)-1-oxo(6-2-hydroisoquinolyl)]acetamide (75 mg, 25%). ES-MS (M+H)+ = 338.

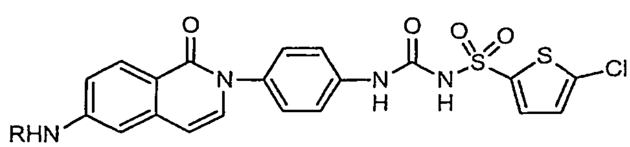
B. Synthesis of N-{2-[4-({[(5-chloro(2-thienyl))sulfonyl]amino}carbonylamino)phenyl]-1-oxo(6-2-hydroisoquinolyl)}-N-methylacetamide

The reduction and coupling steps were performed using the procedures outlined in Scheme 6, steps D and E. ES-MS (M+H)+ = 531, 533 (Cl).

C. Synthesis of {[(5-chloro(2-thienyl))sulfonyl]amino}-N-{4-[6-(methylamino)-1-oxo(2-2-hydroisoquinolyl)]phenyl}carboxamide

To a solution of N-{2-[4-({[(5-chloro(2-thienyl))sulfonyl]amino} carbonylamino)phenyl]-1-oxo(6-2-hydroisoquinolyl)}-N-methylacetamide (35 mg, 0.072 mmol) in methanol (1.2 mL) was added 0.5 M NaOMe (0.44 mL, 0.22 mmol) in methanol. The reaction mixture was stirred at 60 °C overnight, acidified and HPLC purified to give {[(5-chloro(2-thienyl))sulfonyl]amino}-N-{4-[6-(methylamino)-1-oxo(2-2-hydroisoquinolyl)]phenyl} carboxamide (22 mg, 63%). ES-MS (M+H)+ = 489, 491 (Cl).

Examples 383 and 1132-1135



The compounds above where, for example, R = Et, n-Pr, CH_2-c-Pr, CH_2CH_2F and benzyl were synthesized using the procedure outlined in Example 373 for R = Me, varying the alkylating agent in step A.

Example 383

{[(5-chloro(2-thienyl))sulfonyl]amino}-N-{4-[6-(ethylamino)-1-oxo(2-2-hydroisoquinolyl)]-phenyl}carboxamide. ES-MS (M+H)+ = 503, 505 (Cl).

Example 1132

{[(5-chloro(2-thienyl))sulfonyl]amino}-N-{4-[1-oxo-6-(propylamino)(2-2-hydroisoquinolyl)]-phenyl}carboxamide. ES-MS (M+H)+ = 517, 519 (Cl).

Example 1133

{[(5-chloro(2-thienyl))sulfonyl]amino}-N-(4-{6-[(cyclopropylmethyl)amino]-1-oxo(2-2-hydroisoquinolyl)}phenyl)carboxamide. ES-MS (M+H)+ = 529, 531 (Cl).

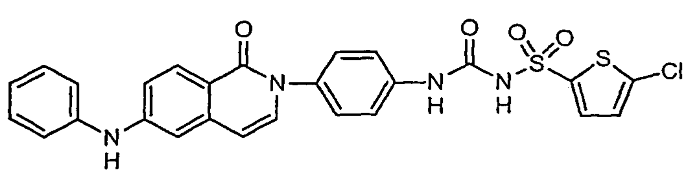
Example 1134

{[(5-chloro(2-thienyl))sulfonyl]amino}-N-(4-{6-[(2-fluoroethyl)amino]-1-oxo(2-2-hydroisoquinolyl)}phenyl)carboxamide. ES-MS (M+H)+ = 521, 523 (Cl).

Example 1135

{[(5-chloro(2-thienyl))sulfonyl]amino}-N-(4-{1-oxo-6-[benzylamino](2-2-hydroisoquinolyl)}-phenyl)carboxamide. ES-MS (M+H)+ = 565, 567 (Cl).

Example 1136



Preparation of {[(5-chloro(2-thienyl))sulfonyl]amino}-N-{4-[1-oxo-6-(phenylamino)(2-2-hydroisoquinolyl)]phenyl}carboxamide

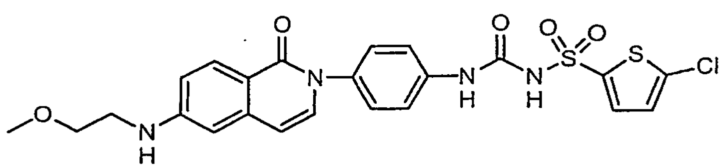
A. 2-(4-nitrophenyl)-6-(phenylamino)-2-hydroisoquinolin-1-one

To a dry RBF under argon was added 6-bromo-2-(4-nitrophenyl)-2-hydroisoquinolin-1-one (66 mg, 0.191 mmol) (prepared as outlined in Example 1125), cesium carbonate (106 mg, 0.325 mmol), tris(dibenzylideneacetone) dipalladium(0) (3.5 mg, 0.076 mmol), 9,9-dimethyl-4,5-bis(diphenylphosphino) xanthene (12 mg, 0.0207 mmol) and neat aniline (0.026 mL, 0.285 mmol). To this flask was added dry dioxane (0.5 mL) and dry toluene (0.5 mL). The reaction was stirred at 80 °C for 5 hr, concentrated and chromatographed on silica gel to give pure 2-(4-nitrophenyl)-6-(phenylamino)-2-hydroisoquinolin-1-one (55 mg, 81%). ES-MS (M+H)+ = 358.

B. {[(5-chloro(2-thienyl))sulfonyl]amino}-N-{4-[1-oxo-6-(phenylamino)(2-2-hydroisoquinolyl)]phenyl}carboxamide

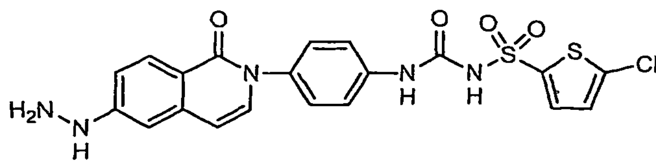
Preparation of the final target was accomplished using the general procedure outlined in Scheme 6, steps D-E, to give the above named sulfonyl urea. ES-MS (M+H)+ = 551, 553 (Cl).

Example 1137



Preparation of {[(5-chloro(2-thienyl))sulfonyl]amino}-N-(4-{6-[(2-methoxyethyl)amino]-1-oxo(2-2-hydroisoquinolyl)}phenyl)carboxamide was accomplished using a similar Buchwald procedure as shown in Example 1136. ES-MS (M+H)+ = 533.0 (Cl).

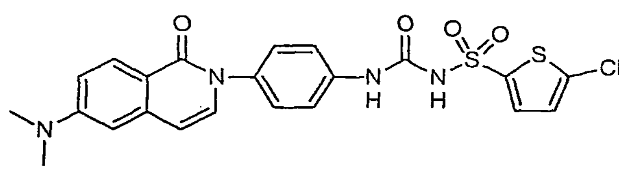
Example 1138



Preparation of {[(5-chloro(2-thienyl))sulfonyl]amino}-N-[4-(6-hydrazino-1-oxo(2-2-hydroisoquinolyl))phenyl]carboxamide

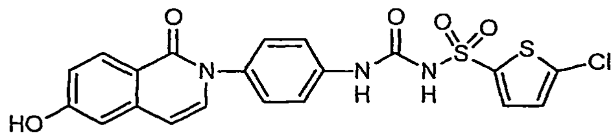
A 5mg (0.011 mmol) sample of {[(5-chloro(2-thienyl))sulfonyl]amino}-N-[4-(6-fluoro-1-oxo(2-2-hydroisoquinolyl))-phenyl]carboxamide was dissolved in 50 μL of neat anhydrous hydrazine and stirred for 18h. The solution was diluted with 250 uL of water and lyophilized to give 3.8 mg (74%) of the desired material. ES-MS (M+H)+ = 490.0 (Cl).

Example 1139



Preparation of N-{4-[6-(dimethylamino)-1-oxo(2-2-hydroisoquinolyl)]phenyl} {[(5-chloro(2-thienyl))sulfonyl]amino}carboxamide: To a suspension of {[(5-chloro(2-thienyl))sulfonyl]amino}-N-{4-[6-(methylamino)-1-oxo(2-2-hydroisoquinolyl)]phenyl}carboxamide (17 mg, 0.035 mmol) (prepared in Example 373) in glacial acetic acid (0.7 mL) was added formaldehyde (12 μL, 0.15 mmol) followed by sodium triacetoxyborohydride (14 mg, 0.067 mmol). The reaction mixture was stirred at 45°C for 2 hr. HPLC purification yielded the final product (7 mg, 40%). ES-MS (M+H)+ = 503, 505 (Cl).

Example 1140



Preparation of {[(5-chloro(2-thienyl))sulfonyl]amino}-N-[4-(6-hydroxy-1-oxo(2-2-hydroisoquinolyl))phenyl]carboxamide:

A. Synthesis of 6-hydroxy-2-(4-nitrophenyl)-2-hydroisoquinolin-1-one

To a solution of 6-methoxy-2-(4-nitrophenyl)-2-hydroisoquinolin-1-one (100 mg, 0.338 mmol) (prepared by the general procedure outline in Scheme 6) in CH_2Cl_2 (3 mL) was added a 1M BBr_3 solution in CH_2Cl_2 (1.35 mL, 1.35 mmol). The solution was refluxed for 18 h, the solvent was removed in vacuo, the residue was triturated with water, and the resulting greenish solid was collected and dried to give 6-hydroxy-2-(4-nitrophenyl)-2-hydroisoquinolin-1-one (89 mg, 93%).

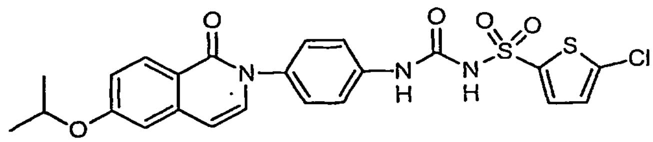
B. Synthesis of 2-(4-aminophenyl)-6-hydroxy-2-hydroisoquinolin-1-one

6-hydroxy-2-(4-nitrophenyl)-2-hydroisoquinolin-1-one was reduced according to the general procedure in Scheme 6 to give the corresponding aniline in 27% yield. ES-MS (M+H)+ = 252.9.

C. Synthesis of {[(5-chloro(2-thienyl))sulfonyl]amino}-N-[4-(6-hydroxy-1-oxo(2-2-hydroisoquinolyl))phenyl]carboxamide

2-(4-aminophenyl)-6-hydroxy-2-hydroisoquinolin-1-one was coupled according to the general procedure outlined in Scheme 6 to give the above named sulfonyl urea. ES-MS (M+H)+ = 476 (Cl).

Example 1141



Preparation of {[(5-chloro(2-thienyl))sulfonyl]amino}-N-{4-[6-(methylethoxy)-1-oxo(2-2-hydroisoquinolyl)]phenyl}carboxamide:

A. Synthesis of 6-(methylethoxy)-2-(4-nitrophenyl)-2-hydroisoquinolin-1-one

To a solution of 6-hydroxy-2-(4-nitrophenyl)-2-hydroisoquinolin-1-one (50 mg, 0.177 mmol) in DMF (0.38 mL) was added 2-bromopropane (0.03 mL) and cesium carbonate (86 mg, 0.267 mmol). After heating at 60 °C for 18h, water was added and the solution stirred and cooled to 0 °C. The precipitate was collected and dried to give 6-(methylethoxy)-2-(4-nitrophenyl)-2-hydroisoquinolin-1-one (34 mg, 59%).

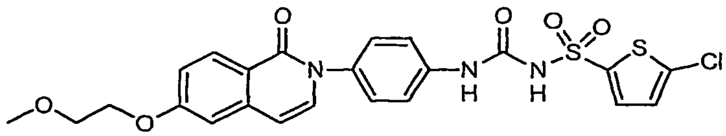
B. Synthesis of 2-(4-aminophenyl)-6-(methylethoxy)-2-hydroisoquinolin-1-one

This material was reduced according to the general procedure in Scheme 6 to give the corresponding aniline in 91% yield. ES-MS (M+H)+ = 295.

C. Synthesis of {[(5-chloro(2-thienyl))sulfonyl]amino}-N-{4-[6-(methylethoxy)-1-oxo(2-2-hydroisoquinolyl)]phenyl}carboxamide

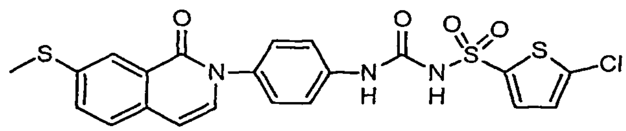
2-(4-aminophenyl)-6-(methylethoxy)-2-hydroisoquinolin-1-one was coupled according to the general procedure outlined in Scheme 6 to give the above named sulfonyl urea. ES-MS (M+H)+ = 518 (Cl); ES-MS (M-H)+ = 516.

Example 1142



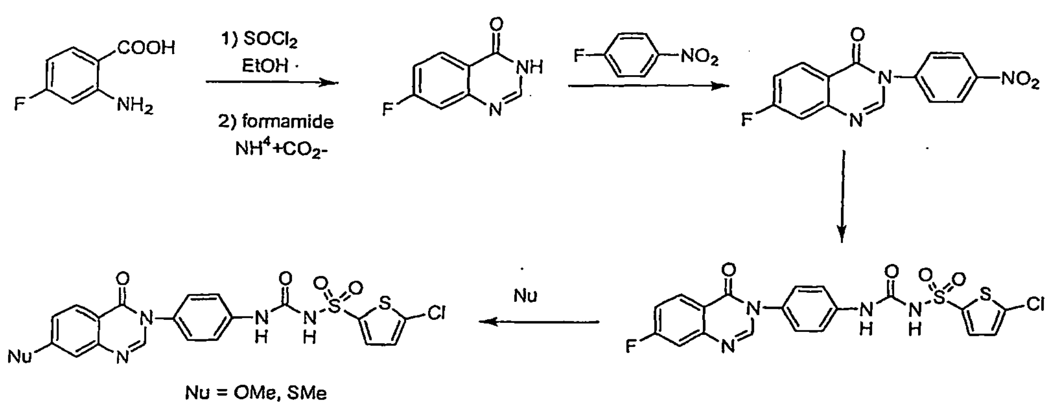
Preparation of {[(5-chloro(2-thienyl))sulfonyl]amino}-N-{4-[6-(2-methoxyethoxy)-1-oxo(2-2-hydroisoquinolyl)]phenyl}carboxamide was accomplished according to the procedure of Example 1141 to give the desired sulfonyl urea. ES-MS (M+H)+ = 534.1 (Cl).

Example 1143

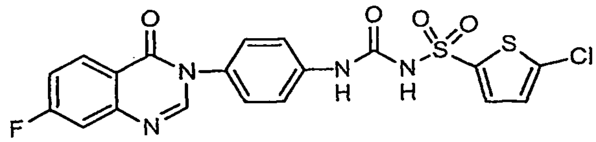


Preparation of {[(5-chloro(2-thienyl))sulfonyl]amino}-N-[4-(7-methylthio-1-oxo(2-2-hydroisoquinolyl))phenyl]carboxamide was accomplished according to the procedure of Example 1145, using {[(5-chloro(2-thienyl))sulfonyl]amino}-N-[4-(7-fluoro-1-oxo(2-2-hydroisoquinolyl))phenyl]-carboxamide as starting material, to give the desire sulfonyl urea. ES-MS (M+H)+ = 506 (Cl).

Scheme 7: General Synthetic Scheme for the Preparation of Quinazolinones:



Example 1144



Preparation of {[(5-chloro(2-thienyl))sulfonyl]amino}-N-[4-(7-fluoro-4-oxo(3-hydroquinazolin-3-yl))phenyl]carboxamide

A. Synthesis of ethyl 2-amino-4-fluorobenzoate

To a chilled solution of 2-amino-4-fluorobenzoic acid (1.57 g, 10.1 mmol) in absolute ethanol (20 mL) was added neat thionyl chloride (4.4 mL, 60 mmol). The reaction mixture was refluxed for 4 days total, with addition of more $SOCl_2$ (8 mL, 110 mmol), then concentrated, diluted with EtOAc, washed with 2N NaOH, dried and concentrated in vacuo to give ethyl 2-amino-4-fluorobenzoate (1.73 g, 94%).

B. Synthesis of 7-fluoro-3-hydroquinazolin-4-one

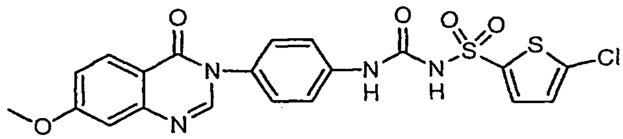
To a suspension of ethyl 2-amino-4-fluorobenzoate (1.73 g, 9.45 mmol) in formamide (8 mL) was added ammonium formate (0.9 g, 14 mmol). The reaction mixture was stirred at 140 °C for 24 hr, with additional ammonium formate (0.92 g, 15 mmol) at 6 hr. The reaction was dilute with EtOAc, washed with water, back-extracted with EtOAc, dried and concentrated in vacuo to give 7-fluoro-3-hydroquinazolin-4-one (2.82 g) which contains some formamide. ES-MS (M+H)+ = 165.

C. Synthesis of {[(5-chloro(2-thienyl))sulfonyl]amino}-N-[4-(7-fluoro-4-oxo(3-hydroquinazolin-3-yl))phenyl]carboxamide

{[(5-chloro(2-thienyl))sulfonyl]amino}-N-[4-(7-fluoro-4-oxo(3-hydroquinazolin-3-yl))phenyl]carboxamide was synthesized from the quinazolinone using the procedures for alkylation, reduction and coupling outlined in Scheme 6, steps C, D and E. The

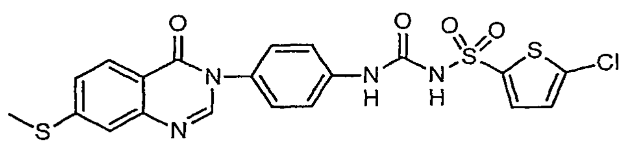
alkylation product was chromatographed on silica gel to remove formamide carried over from the previous step to give pure intermediate in 42% yield. The reduction step was performed in EtOAc instead of EtOH. The coupling proceeded in 50% yield. ES-MS (M+H)+ = 479, 481 (Cl).

Example 507



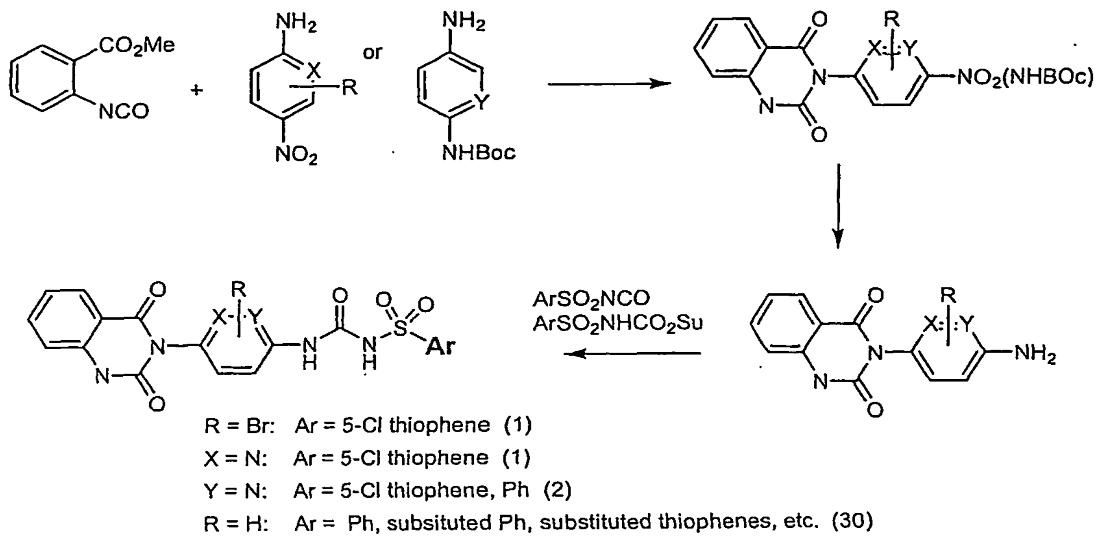
Preparation of {[(5-chloro(2-thienyl))sulfonyl]amino}-N-[4-(7-methoxy-4-oxo(3-hydroquinazolin-3-yl))phenyl]carboxamide: To a solution of {[(5-chloro(2-thienyl))sulfonyl]amino}-N-[4-(7-fluoro-4-oxo(3-hydro-quinazolin-3-yl))phenyl]carboxamide (20 mg, 0.042 mmol) in methanol (0.75 mL) and DMF (0.3 mL) was added 0.5 M NaOMe in MeOH (0.42 mL, 0.21 mmol). The reaction mixture was stirred at 70 °C for 24 hr, acidified and HPLC purified to give pure {[(5-chloro(2-thienyl))sulfonyl]amino}-N-[4-(7-methoxy-4-oxo(3-hydroquinazolin-3-yl))phenyl]carboxamide (7 mg, 33%). ES-MS (M+H)+ = 491, 493 (Cl).

Example 1145

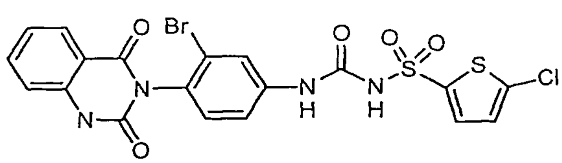


Preparation of {[(5-chloro(2-thienyl))sulfonyl]amino}-N-[4-(7-methylthio-4-oxo(3-hydroquinazolin-3-yl))phenyl]carboxamide: To a solution of {[(5-chloro(2-thienyl))sulfonyl]amino}-N-[4-(7-fluoro-4-oxo(3-hydro-quinazolin-3-yl))phenyl]carboxamide (20 mg, 0.042 mmol) in DMF (0.21 mL) was added NaSMe (7 mg, 0.1 mmol). The reaction mixture was stirred at room temp for 3 hr, acidified and HPLC purified to give pure {[(5-chloro(2-thienyl))sulfonyl]amino}-N-[4-(7-methylthio-4-oxo(3-hydroquinazolin-3-yl))phenyl]carboxamide (17 mg, 80%). ES-MS (M+H)+ = 507, 509 (Cl).

Scheme 8: General synthetic scheme for preparing quinazolinedione-containing sulfonyl ureas



Example 1146



Preparation of N-[4-(2,4-dioxo(1,3-dihydroquinazolin-3-yl))-3-bromophenyl]{[(5-chloro(2-thienyl))sulfonyl]amino}carboxamide

A. Synthesis of 3-(2-bromo-4-nitrophenyl)-1,3-dihydroquinazoline-2,4-dione

To a solution of methyl 2-isocyanatobenzoate (0.266 g, 1.5 mmol) and 2-bromo-4-nitroaniline (0.325 g, 1.5 mmol) in DMF (2 mL) was added DIEA (0.79 mL). The reaction mixture was stirred at room temp for 24 hr, with addition of DBU (0.22 mL) at 17 hr. The reaction mixture was extracted with EtOAc, washed with 1 N HCl and brine, dried and concentrated to give crude product, which was chromatographed on silica gel

with 10% EtOAc/CH_2Cl_2 to give 3-(2-bromo-4-nitrophenyl)-1,3-dihydroquinazoline-2,4-dione (0.24 g, 44%). ES-MS (M+H)+ = 362, 364 (Br).

B. Synthesis of 3-(4-amino-2-bromophenyl)-1,3-dihydroquinazoline-2,4-dione

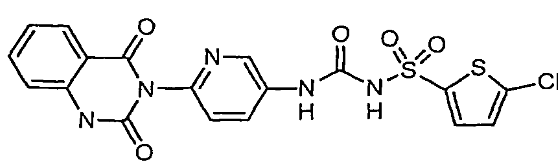
A suspension of 3-(2-bromo-4-nitrophenyl)-1,3-dihydroquinazoline-2,4-dione (0.18 g, 0.5 mmol) and tin(II) chloride dihydrate (0.45 g, 2.0 mmol) in ethyl acetate (5 mL) was heated at 70 °C for 4 hr. The reaction mixture was then cooled, mixed with Celite, made basic with 4N NaOH (3 mL), filtered through Celite, and concentrated in vacuo to give the desired compound (0.155 g, 94%). ES-MS (M+H)+ = 332, 334 (Br).

C. General Procedure for coupling anilines with aryl sulfonamides to form sulfonyl ureas

A solution of the aryl sulfonamide (0.15 mmol) and DSC (0.18 mmol) in CH_2Cl_2 (1 mL) and DBU (45 µL, 0.3 mmol) was stirred at room temp for 16 hr. To this mixture was added the aniline intermediate (0.15 mmol) and CH_3CN (1 mL) and DBU (23 µL, 0.15 mmol) (if aniline is TFA salt). The reaction was heated at 60°C for 17 hr, acidified and HPLC purified to give sulfonyl urea product in typical yields between 25-70%.

Preparation of N-[4-(2,4-dioxo(1,3-dihydroquinazolin-3-yl))-3-bromophenyl]{[(5-chloro(2-thienyl))sulfonyl]amino}carboxamide was achieved in 25% yield. ES-MS (M+H)+ = 556.9. 558.9 (Br, Cl).

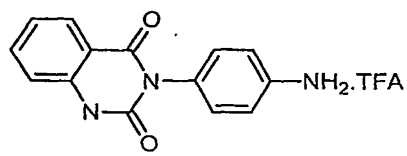
Example 302



Preparation of N-[6-(2,4-dioxo(1,3-dihydroquinazolin-3-yl))(3-pyridyl)]{[(5-chloro(2-thienyl))sulfonyl]amino}carboxamide:

This compound was prepared by first following step A in Example 1146, reacting 2-amino-5-nitropyridine with methyl 2-isocyanatobenzoate. The nitro group was reduced under 1 atm H_2, 10% Pd/C, 1 eq. HCl, MeOH conditions for 6 hr. After filtration and concentration, the aniline was coupled with 5-chlorothiophene-2-sulfonamide using the conditions outlined in step C in Example 1146 to give N-[6-(2,4-dioxo(1,3-dihydroquinazolin-3-yl))(3-pyridyl)]{[(5-chloro(2-thienyl))sulfonyl]amino}carboxamide (47 mg, 33%). ES-MS (M+H)+ = 478, 480 (Cl).

<u>Example 1147</u>



Preparation of 3-(4-aminophenyl)-1,3-dihydroquinazoline-2,4-dione trifluoroacetate salt

A. <u>Synthesis of (tert-butoxy)-N-[4-(2,4-dioxo(1,3-dihydroquinazolin-3-yl))phenyl]carboxamide</u>

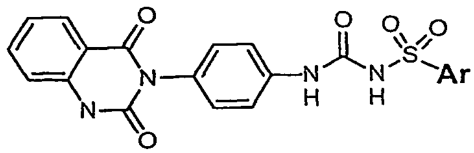
To a solution of methyl 2-isocyanatobenzoate (0.97 g, 5.5 mmol) and Boc 1,4-phenylenediamine (1.04 g, 5 mmol) in THF (15 mL) was added DIEA (0.87 mL, 5 mmol) and DBU (0.75 mL, 5 mmol). The reaction mixture stirred at room temp for 5 hr, the off-white solid filtered and washed with ethyl ether to give desired compound (1.49 g, 85%). ES-MS (M+Na)+ = 376.1, (M-tBu+H)+ = 298.0.

B. <u>Synthesis of 3-(4-aminophenyl)-1,3-dihydroquinazoline-2,4-dione trifluoroacetate salt</u>

To a chilled suspension of (tert-butoxy)-N-[4-(2,4-dioxo(1,3-dihydroquinazolin-3-yl))phenyl]carboxamide (0.35 g, 1 mmol) in CH_2Cl_2 (2 mL) was added neat TFA (2 mL). The resulting solution was stirred cold for 1 hr, concentrated in vacuo, azeotroped

with heptane and dried to give desired compound (0.376 g, 99%) as the mono TFA salt. ES-MS (M+H)+ = 254.

Synthesis of Various Aryl Sulfonylurea Analogs



The sulfonyl urea targets above were prepared using the procedure outlined in Example 1146 Step C, reacting the aniline from Example 1146 with the following 13 commercially available sulfonamides: 5-nitrothiophene-2-sulfonamide; thiophene-2-sulfonamide; 5-chloro-3-methylbenzothiophene-2-sulfonamide; 3,5-dimethylisoxazole-4-sulfonamide; N-(3-methyl-5-sulfamoyl)-3H(1,3,4)thiadiazol-2-ylidene)acetamide; 2,4-dimethyl-1,3-thiazole-5-sulfonamide; 3-bromo-5-chlorothiophene-2-sulfonamide; azetazolamide; 5-isoxazol-3-ylthiophene-2-sulfonamide; 2-chlorobenzenesulfonamide; 3-chlorobenzenesulfonamide; 4-methoxybenzenesulfonamide; 4-(trifluoromethyl)benzene-sulfonamide.

Example 1148

N-[4-(2,4-dioxo(1,3-dihydroquinazolin-3-yl))phenyl]{[(5-nitro(2-thienyl))sulfonyl]-amino}carboxamide. ES-MS (M+H)+ = 488.

Example 1149

N-[4-(2,4-dioxo(1,3-dihydroquinazolin-3-yl))phenyl][(2-thienylsulfonyl)amino]carboxamide. ES-MS (M+H)+ = 443.0.

Example 1150

N-[4-(2,4-dioxo(1,3-dihydroquinazolin-3-yl))phenyl]{[(5-chloro-3-methyl-benzo[b]thiophen-2-yl)sulfonyl]amino}carboxamide. ES-MS (M+H)+ = 541, 543 (Cl).

Example 1151

{[(3,5-dimethylisoxazol-4-yl)sulfonyl]amino}-N-[4-(2,4-dioxo(1,3-dihydroquinazolin-3-yl))phenyl]carboxamide. ES-MS (M+H)+ = 456.

Example 1152

({[2-(1-aza-2-oxopropylidene)-3-methyl(1,3,4-thiadiazolin-5-yl)]sulfonyl}amino)-N-[4-(2,4-dioxo(1,3-dihydroquinazolin-3-yl))phenyl]carboxamide. ES-MS (M+H)+ = 516.

Example 1153

{[(2,4-dimethyl(1,3-thiazol-5-yl))sulfonyl]amino}-N-[4-(2,4-dioxo(1,3-dihydroquinazolin-3-yl))phenyl]carboxamide. ES-MS (M+H)+ = 472.

Example 1154

N-[4-(2,4-dioxo(1,3-dihydroquinazolin-3-yl))phenyl]{[(3-bromo-5-chloro(2-thienyl))-sulfonyl]amino}carboxamide. ES-MS (M+H)+ = 554.8, 556.9, 558.8 (BrCl).

Example 1155

N-{5-[({N-[4-(2,4-dioxo-1,3-dihydroquinazolin-3-yl)phenyl] carbamoyl} amino)sulfonyl]-1,3,4-thiadiazol-2-yl}acetamide. ES-MS (M+H)+ = 502.

Example 1156

N-[4-(2,4-dioxo(1,3-dihydroquinazolin-3-yl))phenyl]{[(5-isoxazol-3-yl(2-thienyl))-sulfonyl]amino}carboxamide. ES-MS (M+H)+ = 510.

Example 1157

N-[4-(2,4-dioxo(1,3-dihydroquinazolin-3-yl))phenyl]{[(2-chlorophenyl) sulfonyl]amino}-carboxamide. ES-MS (M+H)+ = 471, 473 (Cl).

Example 1158

N-[4-(2,4-dioxo(1,3-dihydroquinazolin-3-yl))phenyl]{[(3-chlorophenyl)sulfonyl]-amino}carboxamide. ES-MS (M+H)+ = 471, 473 (Cl).

Example 1159

N-[4-(2,4-dioxo(1,3-dihydroquinazolin-3-yl))phenyl]{[(4-methoxyphenyl)sulfonyl]amino}-carboxamide. ES-MS (M+H)+ = 467.

Example 1160

N-[4-(2,4-dioxo(1,3-dihydroquinazolin-3-yl))phenyl]({[4-(trifluoromethyl)phenyl]-sulfonyl}amino)carboxamide. ES-MS (M+H)+ = 505.

An additional 6 sulfonamides were prepared from the following commercially available sulfonyl chlorides, and were subsequently coupled with the aniline using the procedure in Example 1146 step C: 2-acetamido-4-methyl-5-thiazolesulfonyl chloride; 4-fluorobenzenesulfonyl chloride; 5-(pyrid-2-yl)thiophene-2-sulfonyl chloride; 3,4-dichlorobenzenesulfonyl chloride; 2-(trifluoromethyl)benzenesulfonyl chloride; 3-(trifluoromethyl)benzenesulfonyl chloride.

Example 1161

N-{5-[({N-[4-(2,4-dioxo(1,3-dihydroquinazolin-3-yl))phenyl] carbamoyl} amino)sulfonyl]-4-methyl-1,3-thiazol-2-yl}acetamide. ES-MS (M+H)+ = 515.

Example 1162

N-[4-(2,4-dioxo(1,3-dihydroquinazolin-3-yl))phenyl]{[(4-fluorophenyl) sulfonyl]amino}-carboxamide. ES-MS (M+H)+ = 455.1.

Example 1163

N-[4-(2,4-dioxo(1,3-dihydroquinazolin-3-yl))phenyl]{[(5-(2-pyridyl)(2-thienyl))sulfonyl]-amino}carboxamide. ES-MS (M+H)+ = 520.

Example 1164

{[(3,4-dichlorophenyl)sulfonyl]amino}-N-[4-(2,4-dioxo(1,3-dihydroquinazolin-3-yl))phenyl]carboxamide. ES-MS (M+H)+ = 505, 507 (2Cl).

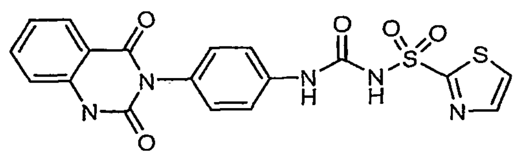
Example 1165

N-[4-(2,4-dioxo(1,3-dihydroquinazolin-3-yl))phenyl]({[2-(trifluoromethyl)phenyl]sulfonyl}-amino)carboxamide. ES-MS (M+H)+ = 505.

Example 1166

N-[4-(2,4-dioxo(1,3-dihydroquinazolin-3-yl))phenyl]({[3-(trifluoromethyl)phenyl]-sulfonyl}amino)carboxamide. ES-MS (M+H)+ = 505.

Example 1167



Preparation of N-[4-(2,4-dioxo(1,3-dihydroquinazolin-3-yl))phenyl][(1,3-thiazol-2-ylsulfonyl)amino]carboxamide

A. Synthesis of (tert-butyl)(1,3-thiazol-2-ylsulfonyl)amine

To a suspension of 2-mercaptothiazole (0.16 g, 1.37 mmol) in CH_2Cl_2 (14 mL) was added water (7 mL) followed by N-chlorosuccinimide (0.75 g, 5.6 mmol). The reaction mixture was stirred vigorously for 1.5 hr, diluted with CH_2Cl_2, washed with sat. $NaHCO_3$, water and brine, dried and concentrated in vacuo to give the crude sulfonyl chloride (0.25 g). A solution of the sulfonyl chloride and t-butylamine (0.75 mL, 7.1 mmol) in THF (2.5 mL) was stirred at room temp for 3 hr. The reaction was diluted with EtOAc, washed with 1N HCl, water and brine, dried and concentrated in vacuo to give desired compound (0.16 g, 53%).

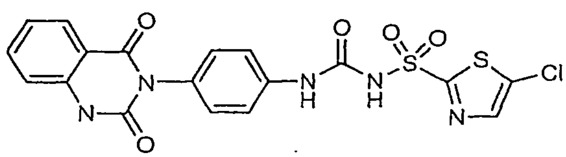
B. Synthesis of 1,3-thiazole-2-sulfonamide

To a solution of (tert-butyl)(1,3-thiazol-2-ylsulfonyl)amine (0.22 g, 1.0 mmol) in 1,2-dichloroethane (10 mL) was added methanesulfonic acid (0.26 mL, 4 mmol). The reaction mixture was heated at 80 °C for 9 hr, concentrated in vacuo and chromatographed to give pure sulfonamide (0.14 g, 88%). ES-MS (M+H)+ = 164.9.

C. Synthesis of N-[4-(2,4-dioxo(1,3-dihydroquinazolin-3-yl))phenyl][(1,3-thiazol-2-ylsulfonyl)amino]carboxamide

The sulfonyl urea was prepared by coupling the aniline from Example 1147 with 1,3-thiazole-2-sulfonamide using the procedure outlined in Example 1146 step C. ES-MS (M+H)+ = 444.0.

Example 1168



Preparation of N-[4-(2,4-dioxo(1,3-dihydroquinazolin-3-yl))phenyl][(5-chloro-1,3-thiazol-2-ylsulfonyl)amino]carboxamide

A. Synthesis of (tert-butyl)[(5-chloro(1,3-thiazol-2-yl))sulfonyl]amine

To a solution of (tert-butyl)(1,3-thiazol-2-ylsulfonyl)amine (0.15 g, 0.7 mmol) in ethyl ether (3 mL) at –78 °C was added a 1.6M solution of n-butyllithium (0.875 mL, 1.4 mmol) in hexanes via syringe under argon. The reaction mixture was stirred at –78 °C for 1 hr, then neat benzenesulfonyl chloride (90 μL, 0.7 mmol) was added. The resulting suspension was stirred at room temp for 2 hr. The reaction was diluted with EtOAc, washed with water and brine, dried, concentrated in vacuo and chromatographed (15% EtOAc/hexane) to give pure desired compound (58 mg, 33%). ES-MS (M+Na)+ = 277, 279 (Cl), (M-tBu+H)+ = 199, 201 (Cl).

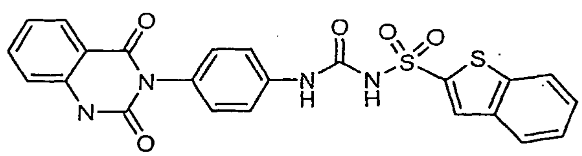
B. Synthesis of 5-chloro-1,3-thiazole-2-sulfonamide

To a solution of (tert-butyl)[(5-chloro(1,3-thiazol-2-yl))sulfonyl]amine (56 mg, 0.22 mmol) in 1,2-dichloroethane (2 mL) was added methanesulfonic acid (50 µL, 0.77 mol). The reaction mixture was heated at 80 °C for 3 hr, concentrated in vacuo and chromatographed (30%EtOAc/hexane) to give pure sulfonamide (42 mg, 96%). ES-MS (M+H)+ = 199 (Cl).

C. Synthesis of N-[4-(2,4-dioxo(1,3-dihydroquinazolin-3-yl))phenyl][(5-chloro-1,3-thiazol-2-ylsulfonyl)amino]carboxamide

The sulfonyl urea was prepared by coupling the aniline from Example 1147 with 5-chloro-1,3-thiazole-2-sulfonamide using the procedure outlined in Example 1146 step C. ES-MS (M+H)+ = 478, 480 (Cl).

Example 1169



Preparation of [(benzo[b]thiophen-2-ylsulfonyl)amino]-N-[4-(2,4-dioxo(1,3-dihydroquinazolin-3-yl))phenyl]carboxamide

A. Synthesis of benzo[b]thiophene-2-sulfonamide

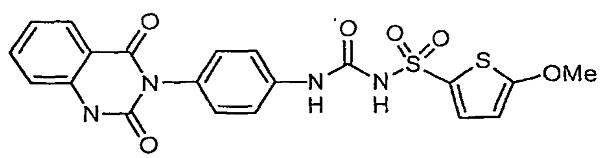
To a solution of benzothiophene (1.63 g, 12.1 mmol) in THF (8 mL) at 0 °C was added a 1.6M solution of n-butyllithium (8.5 mL, 13.6 mmol) in hexanes slowly over 10 min via syringe. The reaction was stirred cold for 10 min. THF (8 mL) was added and the entire reaction was transferred via cannula to a vessel containing sulfuryl chloride (2 mL, 25 mmol) in hexane (8 mL) at 0 °C. The resulting yellow suspension was stirred at 0 °C for 1 hr and eventually became a clear yellow solution. This solution was

concentrated to about 10 mL volume, diluted with acetone (12 mL) and added to a solution of ammonium hydroxide (8 mL) in acetone (25 mL). The reaction mixture was stirred at room temp for 2 hr, added to 200 mL of water on ice bath, acidified with conc. HCl (6 mL). A precipitate was filtered to obtain light yellow solid (1.78 g). This crude product was dissolved in 0.5 N KOH (100 mL) and washed with ethyl ether (50 mL). Upon acidification with conc. HCl (6 mL), the product was extracted into EtOAc (2 x 60 mL), washed with water and brine, dried and concentrated in vacuo to give pure sulfonamide (0.99 g, 39%).

B. Synthesis of [(benzo[b]thiophen-2-ylsulfonyl)amino]-N-[4-(2,4-dioxo(1,3-dihydroquinazolin-3-yl))phenyl]carboxamide

The sulfonyl urea was prepared by coupling the aniline from Example 1147 with benzo[b]thiophene-2-sulfonamide using the procedure outlined in Example 1146 step C. ES-MS (M+H)+ = 493.

Example 1170



Preparation of N-[4-(2,4-dioxo(1,3-dihydroquinazolin-3-yl))phenyl]{[(5-methoxy(2-thienyl))sulfonyl]amino}carboxamide

A. Synthesis of 5-methoxythiophene-2-sulfonamide

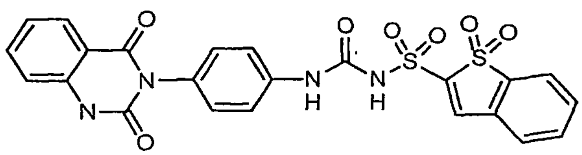
To a solution of 2-methoxythiophene (1 mL, 10 mmol) in dry THF (36 mL) at –78 °C was added a 1.6 M solution of n-butyllithium (8 mL, 12.8 mmol) in hexanes over 10 min via syringe. The reaction was stirred at –78 °C for 2 hr. SO_2 (gas) was bubbled into the reaction mixture for about 10 min, then the reaction was allowed to come to room temp and stirred for 1 hr. A solution of sodium acetate (6.56 g, 80 mmol) and hydroxylamine-O-sulfonic acid (3.14 g, 27.8 mmol) in water (40 mL) was then added,

and the reaction was stirred vigorously for 2 hr. The reaction was basified with 4N NaOH (15 mL), washed with ethyl ether, acidified with 6N HCl (15 mL), extracted with CH_2Cl_2, washed with water and brine, dried and concentrated in vacuo to give pure sulfonamide (1.01 g, 53%). ES-MS (M+H)+ = 194.

B. Synthesis of N-[4-(2,4-dioxo(1,3-dihydroquinazolin-3-yl))phenyl]{[(5-methoxy(2-thienyl))sulfonyl]amino}carboxamide

The sulfonyl urea was prepared by coupling the aniline from Example 1147 with 5-methoxythiophene-2-sulfonamide using the procedure outlined in Example 1146 step C. ES-MS (M+H)+ = 473.

Example 1171



Preparation of N-[4-(2,4-dioxo(1,3-dihydroquinazolin-3-yl))phenyl]{[(1,1-dioxobenzo[d]thiol-2-yl)sulfonyl]amino}carboxamide

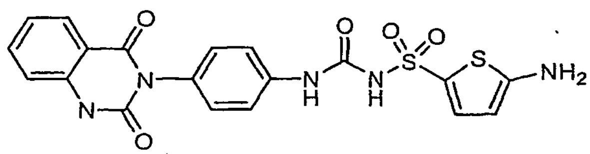
A. Synthesis of N-[4-(1,3-dioxobenzo[c]azolidin-2-yl)naphthyl]{[(5-chloro(2-thienyl))sulfonyl]amino}carboxamide

To a solution of the sulfonamide from Example 7 (0.213 g, 1 mmol) in CH_2Cl_2 (4 mL) was added m-chloroperbenzoic acid (0.49 g, 2.2 mmol). The reaction mixture was refluxed for 20 hr, diluted with EtOAc, washed with 5% $NaHCO_3$, 1N HCl and brine, dried and concentrated in vacuo to give sulfonamide (0.17 g, 71%). ES-MS (M+H)+ = 246.

B. Synthesis of N-[4-(2,4-dioxo(1,3-dihydroquinazolin-3-yl))phenyl]{[(1,1-dioxobenzo[d]thiol-2-yl)sulfonyl]amino}carboxamide

The sulfonyl urea was prepared by coupling the aniline from Example 1147 with N-[4-(1,3-dioxobenzo[c]azolidin-2-yl)naphthyl]{[(5-chloro(2-thienyl))sulfonyl]amino}carboxamide using the procedure outlined in Example 1146 step C. ES-MS (M+H)+ = 525.

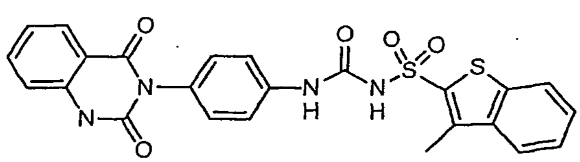
Example 1172



Preparation of {[(5-amino(2-thienyl))sulfonyl]amino}-N-[4-(2,4-dioxo(1,3-dihydroquinazolin-3-yl))phenyl]carboxamide

To a solution of N-[4-(2,4-dioxo(1,3-dihydroquinazolin-3-yl))phenyl]{[(5-nitro(2-thienyl))sulfonyl]amino}carboxamide (from Example 1148) (20 mg, 0.041 mmol) in methanol (1.5 mL) and triethylamine (11 µL, 0.08 mmol) was added 10% Pd/C (5 mg, 0.005 mmol) under argon. The reaction mixture was hydrogenated under 1 atm H_2 for 3 hr, filtered, concentrated and HPLC purified to give the aniline (6 mg, 33%). ES-MS (M+H)+ = 458.

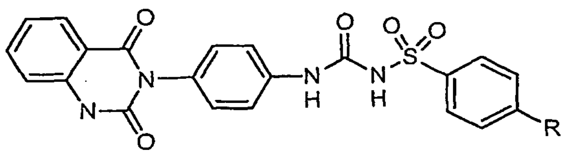
Example 1173



Preparation of N-[4-(2,4-dioxo(1,3-dihydroquinazolin-3-yl))phenyl]{[(3-methylbenzo[b]thiophen-2-yl)sulfonyl]amino}carboxamide

To a solution of the sulfonylurea from Example 1150 (52 mg, 0.046 mmol) in methanol (1.5 mL) and triethylamine (12 µL) was added 10% Pd/C (50 mg) and PtO_2 (7 mg). The reaction mixture was hydrogenated under 250 psi H_2 for 4 days, filtered, concentrated and HPLC purified to give the dehalogenated product (2 mg, 10%). ES-MS (M+H)+ = 507.

Examples 1174-1176



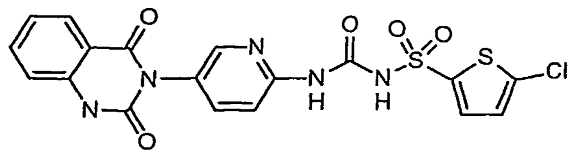
The sulfonyl urea targets above were prepared by reaction of the aniline 3-(4-aminophenyl)-1,3-dihydroquinazoline-2,4-dione trifluoroacetate salt (Example 1147) with 3 commercially available substituted phenylsulfonylisocyanates (1.5 eq.) (R = H, Cl, CH_3) in DMF. Products were typically isolated by precipitation from DMF reaction mixture with water and filtration.

Example 1174
N-[4-(2,4-dioxo(1,3-dihydroquinazolin-3-yl))phenyl][(phenylsulfonyl)amino]carboxamide. ES-MS (M+H)+ = 437.0.

Example 1175
N-[4-(2,4-dioxo(1,3-dihydroquinazolin-3-yl))phenyl]{[(4-chlorophenyl)sulfonyl]amino} carboxamide. ES-MS (M+H)+ = 471, 473 (Cl).

Example 1176
N-[4-(2,4-dioxo(1,3-dihydroquinazolin-3-yl))phenyl]{[(4-methylphenyl)sulfonyl]amino} carboxamide. ES-MS (M+H)+ = 451.

Example 1177



Preparation of N-[5-(2,4-dioxo(1,3-dihydroquinazolin-3-yl))(2-pyridyl)]{[(5-chloro(2-thienyl))sulfonyl]amino}carboxamide

A. Synthesis of (tert-butoxy)-N-(5-nitro(2-pyridyl))carboxamide

To a solution of 2-amino-5-nitropyridine (0.555 g, 4 mmol) in THF (10 mL) was added 1M NaHMDS in THF (8 mL, 8 mmol). The resulting dark red suspension was stirred for 15 min, followed by addition of a solution of Boc anhydride (0.87 mL, 3.8 mmol) in THF (5 mL). The reaction mixture was stirred at room temp for 21 hr, dilute with EtOAc, washed with 1N HCl and brine, dried and concentrated in vacuo to give desired compound (0.63 g, 70%). ES-MS (M+H)+ = 240, (M-tBu+H)+ = 184.

B. Synthesis of N-(5-amino(2-pyridyl))(tert-butoxy)carboxamide

To a suspension of (tert-butoxy)-N-(5-nitro(2-pyridyl))carboxamide (0.27 g, 1.13 mmol) in methanol (2 mL), ethyl acetate (4 mL) and TEA (0.16 mL) was added 10% Pd/C (60 mg, 0.056 mmol) under argon. The reaction mixture was hydrogenated under 1 atm H_2 for 20 hr, filtered through Celite and concentrated in vacuo to give desired compound (0.226 g, 97%).

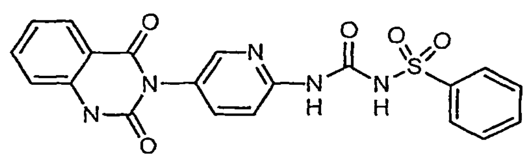
C. Synthesis of [(tert-butyl)amino]-N-[5-(2,4-dioxo(1,3-dihydroquinazolin-3-yl))(2-pyridyl)]carboxamide

The above named compound was prepared using the procedure outlined in Example 1146 step A by reaction of N-(5-amino(2-pyridyl))(tert-butoxy)carboxamide with methyl 2-isocyanatobenzoate. ES-MS (M+H)+ = 355.

D. Synthesis of N-[5-(2,4-dioxo(1,3-dihydroquinazolin-3-yl))(2-pyridyl)]{[(5-chloro(2-thienyl))sulfonyl]amino}carboxamide

To a solution of 5-chlorothiophene-2-sulfonamide (20 mg, 0.1 mmol) and [(tert-butyl)amino]-N-[5-(2,4-dioxo(1,3-dihydroquinazolin-3-yl))(2-pyridyl)]carboxamide (35 mg, 0.1 mmol) in DMF (1 mL) was added DBU (30 μL). The reaction mixture was heated at 90 °C for 3 days, acidified and HPLC purified to give the sulfonyl urea (7 mg, 16%). ES-MS (M+H)+ = 478, 480 (Cl).

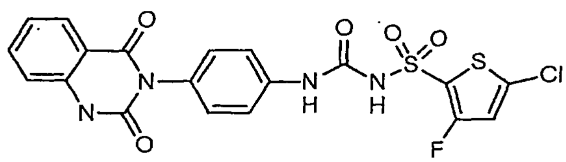
Example 1178



Preparation of N-[5-(2,4-dioxo(1,3-dihydroquinazolin-3-yl))(2-pyridyl)] [(phenylsulfonyl)amino]carboxamide

This compound was prepared by TFA deprotection of [(tert-butyl)amino]-N-[5-(2,4-dioxo(1,3-dihydroquinazolin-3-yl))(2-pyridyl)]carboxamide from Example 1177, step C, followed by reaction of the aminopyridine with phenylsulfonylisocyanate (1.5 eq) in DMF, precipitation from 0.1% TFA and filtration of product to give the sulfonyl urea desired compound (40% yield). ES-MS (M+H)+ = 438.

Example 1179



N-[4-(2,4-dioxo(1,3-dihydroquinazolin-3-yl))phenyl]{[(5-chloro-3-fluoro(2-thienyl))sulfonyl]amino}carboxamide

A. Synthesis of (tert-butyl)[(5-chloro(2-thienyl))sulfonyl]amine

A solution of 5.5 g (27.5 mmol) of 5-chlorothiophenesulfonyl chloride in dry THF at 0°C was treated with a solution of 5.7 mL (75.5 mmol) of t-butylamine. After warming to 23°C, the reaction mixture was diluted with 125 mL of diethyl ether, filtered, and washed with 1 N HCl, brine, and dried ($MgSO_4$). Concentration in vacuo affords 6.4 g (98%) of the named compound as an oil.

B. Synthesis of (tert-butyl)[(5-chloro-3-fluoro(2-thienyl))sulfonyl]amine

A THF solution (1.5 mL) of 128 mg (0.50 mmol) of (tert-butyl)[(5-chloro(2-thienyl))sulfonyl]amine was cooled to −78°C and treated with 954 μL (1.5 mmol) of a 1.6 M solution of butyl lithium in hexane. After 1 h, 159 mg (0.5 mmol) of bis(phenylsulfonyl)fluoroamine was added and the solution was allowed to warm to 23 °C. The reaction was quenched with 1 mL of sat. NH_4Cl, extracted 3 times with diethyl ether, dried ($MgSO_4$), concentrated in vacuo to afford a quantitative yield (147 mg) of the desire product. ^{19}F-NMR ($CDCl_3$) δ (ppm): −113.4 .

C. Synthesis of N-[4-(2,4-dioxo(1,3-dihydroquinazolin-3-yl))phenyl]{[(5-chloro-3-fluoro(2-thienyl))sulfonyl]amino}carboxamide

A 19 mg-sample (0.07 mmol) of (tert-butyl)[(5-chloro-3-fluoro(2-thienyl))sulfonyl]amine was dissolved in neat TFA and stirred for 1 h, concentrated in vacuo and used directly in the next transformation. This sample was dissolved in 150 uL of DCM and 21 mg (0.084 mmol) of DSC was added followed by 21 μL (0.14 mmol) of DBU. This solution was stirred for 18h, 26 mg (0.07) of 3-(4-aminophenyl)-1,3-dihydroquinazoline-2,4-dione trifluoroacetate salt was added plus 150 μL of dry acetonitrile and refluxed for 2h. This material was then purified on RP-HPLC to afford 11 mg (34%) of the desired product. ES-MS: M+H+= 495 (Cl).

Pharmaceutical Compositions and Methods of Treatment

A compound of formulae (I)-(VIII) according to the invention may be formulated into pharmaceutical compositions. Accordingly, the invention also relates to a pharmaceutical composition for preventing or treating thrombosis in a mammal, particularly those pathological conditions involving platelet aggregation, containing a therapeutically effective amount of a compound of formulae (I)-(VIII) or a pharmaceutically acceptable salt thereof, each as described above, and a pharmaceutically acceptable carrier or agent. Preferably, a pharmaceutical composition of the invention contains a compound of formulae (I)-(VIII), or a salt thereof, in an amount effective to inhibit platelet aggregation, more preferably, ADP-dependent aggregation, in a mammal, in particular, a human. Pharmaceutically acceptable carriers or agents include those known in the art and are described below.

Pharmaceutical compositions of the invention may be prepared by mixing the compound of formulae (I)-(VIII) with a physiologically acceptable carrier or agent. Pharmaceutical compositions of the invention may further include excipients, stabilizers, diluents and the like and may be provided in sustained release or timed release formulations. Acceptable carriers, agents, excipients, stablilizers, diluents and the like for therapeutic use are well known in the pharmaceutical field, and are described, for example, in *Remington's Pharmaceutical Sciences*, Mack Publishing Co., ed. A.R. Gennaro (1985). Such materials are nontoxic to the recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, acetate and other organic acid salts, antioxidants such as ascorbic acid, low molecular weight (less than about ten residues) peptides such as polyarginine, proteins, such as serum albumin, gelatin, or immunoglobulins, hydrophilic polymers such as polyvinylpyrrolidinone, amino acids such as glycine, glutamic acid, aspartic acid, or arginine, monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, mannose or dextrins, chelating agents such as EDTA, sugar alcohols such as mannitol or sorbitol, counterions such as sodium and/or nonionic surfactants such as TWEEN, or polyethyleneglycol.

Methods for preventing or treating thrombosis in a mammal embraced by the invention administer a therapeutically effective amount of a compound of formulae (I)-

(VIII) alone or as part of a pharmaceutical composition of the invention as described above to a mammal, in particular, a human. Compounds of formulae (I)-(VIII) and pharmaceutical compositions of the invention containing a compound of formulae (I)-(VIII) of the invention are suitable for use alone or as part of a multi-component treatment regimen for the prevention or treatment of cardiovascular diseases, particularly those related to thrombosis. For example, a compound or pharmaceutical composition of the invention may be used as a drug or therapeutic agent for any thrombosis, particularly a platelet-dependent thrombotic indication, including, but not limited to, acute myocardial infarction, unstable angina, chronic stable angina, transient ischemic attacks, strokes, peripheral vascular disease, preeclampsia/eclampsia, deep venous thrombosis, embolism, disseminated intravascular coagulation and thrombotic cytopenic purpura, thrombotic and restenotic complications following invasive procedures, e.g., angioplasty, carotid endarterectomy, post CABG (coronary artery bypass graft) surgery, vascular graft surgery, stent placements and insertion of endovascular devices and protheses.

Compounds and pharmaceutical compositions of the invention may also be used as part of a multi-component treatment regimen in combination with other therapeutic or diagnostic agents in the prevention or treatment of thrombosis in a mammal. In certain preferred embodiments, compounds or pharmaceutical compositions of the invention may be coadministered along with other compounds typically prescribed for these conditions according to generally accepted medical practice such as anticoagulant agents, thrombolytic agents, or other antithrombotics, including platelet aggregation inhibitors, tissue plasminogen activators, urokinase, prourokinase, streptokinase, heparin, aspirin, or warfarin. Coadministration may also allow for application of reduced doses of the thrombolytic agents and therefore minimize potential hemorrhagic side-effects. Compounds and pharmaceutical compositions of the invention may also act in a synergistic fashion to prevent reocclusion following a successful thrombolytic therapy and/or reduce the time to reperfusion.

The compounds and pharmaceutical compositions of the invention may be utilized *in vivo*, ordinarily in mammals such as primates, (e.g., humans), sheep, horses, cattle, pigs, dogs, cats, rats and mice, or *in vitro*. The biological properties, as defined

above, of a compound or a pharmaceutical composition of the invention can be readily characterized by methods that are well known in the art such as, for example, by *in vivo* studies to evaluate antithrombotic efficacy, and effects on hemostasis and hematological parameters.

Compounds and pharmaceutical compositions of the invention may be in the form of solutions or suspensions. In the management of thrombotic disorders the compounds or pharmaceutical compositions of the invention may also be in such forms as, for example, tablets, capsules or elixirs for oral administration, suppositories, sterile solutions or suspensions or injectable administration, and the like, or incorporated into shaped articles. Subjects (typically mammalian) in need of treatment using the compounds or pharmaceutical compositions of the invention may be administered dosages that will provide optimal efficacy. The dose and method of administration will vary from subject to subject and be dependent upon such factors as the type of mammal being treated, its sex, weight, diet, concurrent medication, overall clinical condition, the particular compound of formulae (I)-(VIII) employed, the specific use for which the compound or pharmaceutical composition is employed, and other factors which those skilled in the medical arts will recognize.

Dosage formulations of compounds of formulae (I)-(VIII), or pharmaceutical compositions contain a compound of the invention, to be used for therapeutic administration must be sterile. Sterility is readily accomplished by filtration through sterile membranes such as 0.2 micron membranes, or by other conventional methods. Formulations typically will be stored in a solid form, preferably in a lyophilized form. While the preferred route of administration is orally, the dosage formulations of compounds of formulae (I)-(VIII) or pharmaceutical compositions of the invention may also be administered by injection, intravenously (bolus and/or infusion), subcutaneously, intramuscularly, colonically, rectally, nasally, transdermally or intraperitoneally. A variety of dosage forms may be employed as well including, but not limited to, suppositories, implanted pellets or small cylinders, aerosols, oral dosage formulations and topical formulations such as ointments, drops and dermal patches. The compounds of formulae (I)-(VIII) and pharmaceutical compositions of the invention may also be

incorporated into shapes and articles such as implants which may employ inert materials such biodegradable polymers or synthetic silicones as, for example, SILASTIC, silicone rubber or other polymers commercially available. The compounds and pharmaceutical compositions of the invention may also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of lipids, such as cholesterol, stearylamine or phosphatidylcholines.

Therapeutically effective dosages may be determined by either *in vitro* or *in vivo* methods. For each particular compound or pharmaceutical composition of the invention, individual determinations may be made to determine the optimal dosage required. The range of therapeutically effective dosages will be influenced by the route of administration, the therapeutic objectives and the condition of the patient. For injection by hypodermic needle, it may be assumed the dosage is delivered into the bodily fluids. For other routes of administration, the absorption efficiency must be individually determined for each compound by methods well known in pharmacology. Accordingly, it may be necessary for the therapist to titer the dosage and modify the route of administration as required to obtain the optimal therapeutic effect.

The determination of effective dosage levels, that is, the dosage levels necessary to achieve the desired result, i.e., platelet ADP receptor inhibition, will be readily determined by one skilled in the art. Typically, applications of a compound or pharmaceutical composition of the invention are commenced at lower dosage levels, with dosage levels being increased until the desired effect is achieved. The compounds and compositions of the invention may be administered orally in an effective amount within the dosage range of about 0.01 to 1000 mg/kg in a regimen of single or several divided daily doses. If a pharmaceutically acceptable carrier is used in a pharmaceutical composition of the invention, typically, about 5 to 500 mg of a compound of formulae (I)-(VIII) is compounded with a pharmaceutically acceptable carrier as called for by accepted pharmaceutical practice including, but not limited to, a physiologically acceptable vehicle, carrier, excipient, binder, preservative, stabilizer, dye, flavor, etc.

The amount of active ingredient in these compositions is such that a suitable dosage in the range indicated is obtained.

Typical adjuvants which may be incorporated into tablets, capsules and the like include, but are not limited to, binders such as acacia, corn starch or gelatin, and excipients such as microcrystalline cellulose, disintegrating agents like corn starch or alginic acid, lubricants such as magnesium stearate, sweetening agents such as sucrose or lactose, or flavoring agents. When a dosage form is a capsule, in addition to the above materials it may also contain liquid carriers such as water, saline, or a fatty oil. Other materials of various types may be used as coatings or as modifiers of the physical form of the dosage unit. Sterile compositions for injection can be formulated according to conventional pharmaceutical practice. For example, dissolution or suspension of the active compound in a vehicle such as an oil or a synthetic fatty vehicle like ethyl oleate, or into a liposome may be desired. Buffers, preservatives, antioxidants and the like can be incorporated according to accepted pharmaceutical practice.

Pharmacological Assays

The pharmacological activity of each of the compounds according to the invention is determined by the following *in vitro* assays:

I. Inhibition of ADP-Mediated Platelet Aggregation *in vitro*

The effect of testing the compound according to the invention on ADP-induced human platelet aggregation is preferably assessed in 96-well microtiter assay (see generally the procedures in Jantzen, H.M. et al. (1999) *Thromb. Hemost.* 81:111-117). Human venous blood is collected from healthy, drug-free volunteers into ACD (85 mM sodium citrate, 111 mM glucose, 71.4 mM citric acid) containing PGI_2 (1.25 ml ACD containing 1.6 μM PGI_2/10 ml blood; PGI_2 was from Sigma, St. Louis, MO). Platelet-rich plasma (PRP) is prepared by centrifugation at 160 x g for 20 minutes at room temperature. Washed platelets are prepared by centrifuging PRP for 10 minutes at 730 g and resuspending the platelet pellet in CGS (13 mM sodium citrate, 30 mM glucose, 120 mM NaCl; 2 ml CGS/10 ml original blood volume) containing 1U/ml apyrase (grade V, Sigma, St. Louis, MO). After incubation at 37 °C for 15 minutes, the platelets are

collected by centrifugation at 730 g for 10 minutes and resuspended at a concentration of $3x10^8$ platelets/ml in Hepes-Tyrode's buffer (10 mM Hepes, 138 mM NaCl, 5.5 mM glucose, 2.9 mM KCl, 12 mM $NaHCO_3$, pH 7.4) containing 0.1% bovine serum albumin, 1 mM $CaCl_2$ and 1 mM $MgCl_2$. This platelet suspension is kept >45 minutes at 37 °C before use in aggregation assays.

Inhibition of ADP-dependent aggregation is preferably determined in 96-well flat-bottom microtiter plates using a microtiter plate shaker and plate reader similar to the procedure described by Frantantoni et al., *Am. J. Clin. Pathol.* 94, 613 (1990). All steps are performed at room temperature. The total reaction volume of 0.2 ml/well includes in Hepes-Tyrodes buffer/0.1% BSA: 4.5 x 10^7 apyrase-washed platelets, 0.5 mg/ml human fibrinogen (American Diagnostica, Inc., Greenwich, CT), serial dilutions of test compounds (buffer for control wells) in 0.6% DMSO. After about 5 minutes preincubation at room temperature, ADP is added to a final concentration of 2 :M which induces submaximal aggregation. Buffer is added instead of ADP to one set of control wells (ADP^- control). The OD of the samples is then determined at 490 nm using a microtiter plate reader (Softmax, Molecular Devices, Menlo Park, CA) resulting in the 0 minute reading. The plates are then agitated for 5 min on a microtiter plate shaker and the 5 minute reading is obtained in the plate reader. Aggregation is calculated from the decrease of OD at 490 nm at t = 5 minutes compared to t = 0 minutes and is expressed as % of the decrease in the ADP control samples after correcting for changes in the unaggregated control samples.

II. <u>Inhibition of [^{3}H]2-MeS-ADP Binding to Platelets</u>

Having first determined that the compounds according to the invention inhibit ADP-dependent platelet aggregation with the above assay, a second assay is used to determine whether such inhibition is mediated by interaction with platelet ADP receptors. Utilizing the second assay the potency of inhibition of such compounds with respect to [^{3}H]2-MeS-ADP binding to whole platelets is determined. [^{3}H]2-MeS-ADP binding experiments are routinely performed with outdated human platelets collected by standard

procedures at hospital blood banks. Apyrase-washed outdated platelets are prepared as follows (all steps at room temperature, if not indicated otherwise):

Outdated platelet suspensions are diluted with 1 volume of CGS and platelets pelleted by centrifugation at 1900 x g for 45 minutes. Platelet pellets are resuspended at 3-6x10^9 platelets /ml in CGS containing 1 U/ml apyrase (grade V, Sigma, St. Louis, MO) and incubated for 15 minutes at 37°C. After centrifugation at 730 x g for 20 minutes, pellets are resuspended in Hepes-Tyrode's buffer containing 0.1% BSA (Sigma, St. Louis, MO) at a concentration of 6.66x10^8 platelets/ml. Binding experiments are performed after > 45 minutes resting of the platelets.

Alternatively, binding experiments are performed with fresh human platelets prepared as described in I.(Inhibition of ADP-Mediated Platelet Aggregation in vitro), except that platelets are resuspended in Hepes-Tyrode's buffer containing 0.1% BSA (Sigma , St. Louis, MO) at a concentration of 6.66x10^8 platelets/ml. Very similar results are obtained with fresh and outdated platelets.

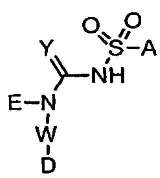
A platelet ADP receptor binding assay using the tritiated potent agonist ligand [^{3}H]2-MeS-ADP (Jantzen, H.M. et al. (1999) Thromb. Hemost. 81:111-117) has been adapted to the 96-well microtiter format. In an assay volume of 0.2 ml Hepes-Tyrode's buffer with 0.1% BSA and 0.6% DMSO, 1x10^8 apyrase-washed platelets are preincubated in 96-well flat bottom microtiter plates for 5 minutes with serial dilutions of test compounds before addition of 1nM [^{3}H]2-MeS-ADP ([^{3}H]2-methylthioadenosine-5'-diphosphate, ammonium salt; specific activity 48-49 Ci/mmole, obtained by custom synthesis from Amersham Life Science, Inc., Arlington Heights, IL, or NEN Life Science Products, Boston, MA). Total binding is determined in the absence of test compounds. Samples for nonspecific binding may contain 10^{-5} M unlabelled 2-MeS-ADP (RBI, Natick, MA). After incubation for 15 minutes at room temperature, unbound radioligand is separated by rapid filtration and two washes with cold (4-8 °C) Binding Wash Buffer (10 mM Hepes pH 7.4, 138 mM NaCl) using a 96-well cell harvester (Minidisc 96, Skatron Instruments, Sterling, VA) and 8x12 GF/C glassfiber filtermats (Printed Filtermat A, for 1450 Microbeta, Wallac Inc., Gaithersburg, MD). The platelet-bound

radioactivity on the filtermats is determined in a scintillation counter (Microbeta 1450, Wallac Inc., Gaithersburg, MD). Specific binding is determined by subtraction of non-specific binding from total binding, and specific binding in the presence of test compounds is expressed as % of specific binding in the absence of test compounds dilutions.

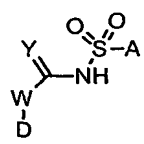
It should be understood that the foregoing discussion, embodiments and examples merely present a detailed description of certain preferred embodiments. It will be apparent to those of ordinary skill in the art that various modifications and equivalents can be made without departing from the spirit and scope of the invention. All the patents, journal articles and other documents discussed or cited above are herein incorporated by reference.

WHAT IS CLAIMED IS:

1. A compound selected from the group consisting of formula (I), formula (II), formula (III), formula (IV), formula (V), formula (VI), formula (VII) and formula (VIII):



I



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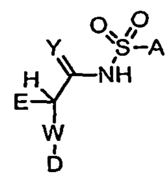

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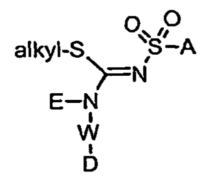

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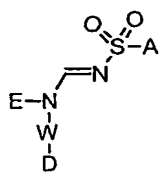

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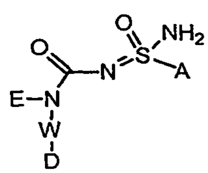

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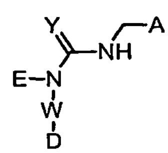

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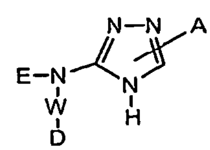


VIII

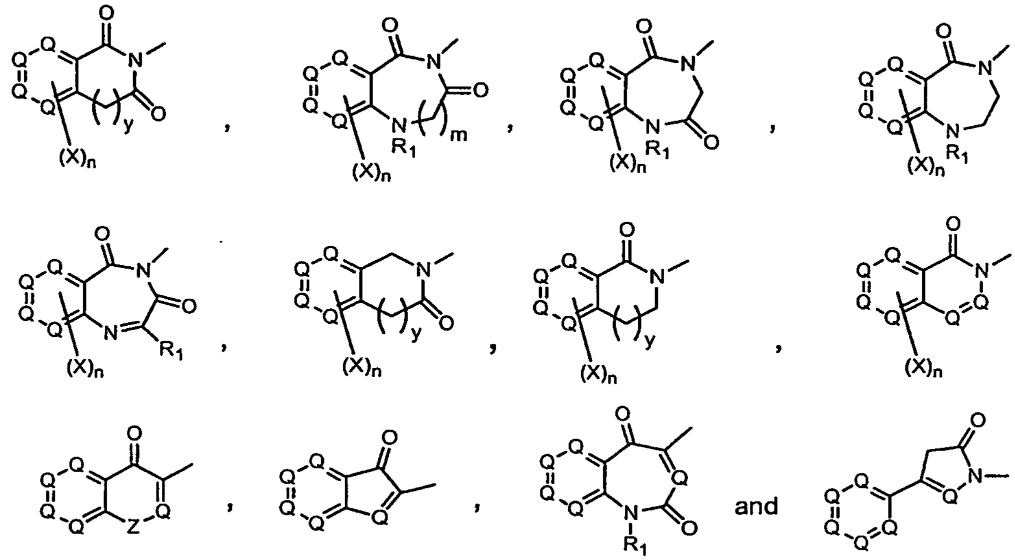
wherein:

A is selected from the group consisting of aryl, substituted aryl, heteroaryl, substituted heteroaryl, alkylaryl, and alkylheteroaryl;

W is selected from the group consisting of aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

E is selected from the group consisting of H, $-C_1-C_8$ alkyl, polyhaloalkyl, $-C_{3-8}$-cycloalkyl, aryl, alkylaryl, substituted aryl, heteroaryl, and substituted heteroaryl;

D is selected from the group consisting of $-NR^1-(C{=}O)-R^2$, $-O-R^1$;



wherein:

R^1 is independently selected from the group consisting of:

H, C_1-C_8 alkyl, polyhaloalkyl, -C_{3-8}-cycloalkyl, aryl, alkylaryl, substituted aryl, heteroaryl, substituted heteroaryl, -(C=O)-C_1-C_8 alkyl, -(C=O)-aryl, -(C=O)-substituted aryl, -(C=O)-heteroaryl and -(C=O)-substituted heteroaryl;

R^2 is independently selected from the group consisting of: aryl, substituted aryl, heteroaryl, and substituted heteroaryl, or

R^1 and R^2 can be direct linked or can be indirectly linked through a carbon chain that is from 1 to about 8 carbon atoms in length,

n is an integer from 0-4,

m is an integer from 0 or 1,

y is an integer from 0-4 and

Q is independently C or N, wherein when Q is a ring carbon atom, each ring carbon atom is independently substituted by X, wherein

X is in each case a member independently selected from the group consisting of:

hydrogen, halogen, polyhaloalkyl, $-OR^3$, $-SR^3$, -CN, $-NO_2$, $-SO_2R^3$, $-C_{1-10}$-alkyl, $-C_{3-8}$-cycloalkyl, aryl, aryl-substituted by 1-4 R^3 groups, amino, amino-C_{1-8}-alkyl, C_{1-3}-acylamino, C_{1-3}-acylamino-C_{1-8}-alkyl, C_{1-6}-alkylamino, C_{1-6}-alkylamino C_{1-8} alkyl, C_{1-6} dialkylamino, C_{1-6} dialkylamino C_{1-8} alkyl, C_{1-6} alkoxy, C_{1-6} alkoxy-C_{1-6}-alkyl, carboxy-C_{1-6}-alkyl, C_{1-3}-alkoxycarbonyl, C_{1-3}-alkoxycarbonyl- C_{1-6}-alkyl, carboxy C_{1-6} alkyloxy, hydroxy, hydroxy C_{1-6} alkyl, and a 5 to 10 membered fused or non-fused aromatic or nonaromatic heterocyclic ring system, having 1 to 4 heteroatoms independently selected from N, O, and S, with the proviso that the carbon and nitrogen atoms, when present in the heterocyclic ring system, are unsubstituted, mono- or di-substituted independently with 0-2 R^4 groups,

wherein R^3 and R^4 are each independently selected from the group consisting of:

hydrogen, halogen, -CN, $-NO_2$, $-C_{1-10}$ alkyl, C_{3-8}-cycloalkyl, aryl, amino, amino-C_{1-8}-alkyl, C_{1-3}-acylamino, C_{1-3}-acylamino-C_{1-8}-alkyl, C_{1-6}-alkylamino, C_{1-6}-alkylamino C_{1-8} alkyl, C_{1-6} dialkylamino, C_{1-6} dialkylamino C_{1-8} alkyl, C_{1-6} alkoxy, C_{1-6} alkoxy-C_{1-6}-alkyl, carboxy-C_{1-6}-alkyl, C_{1-3}-alkoxycarbonyl, C_{1-3}-alkoxycarbonyl-C_{1-6}-alkyl, carboxy-C_{1-6}-alkyloxy, hydroxy, hydroxy-C_{1-6}-alkyl, -thio and thio-C_{1-6}-alkyl;

Y is selected from the group consisting of O, S, N-OR^5, and NR^5,

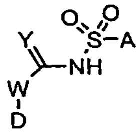
wherein R^5 is selected from the group consisting of :

H, C_{1-10} alkyl, C_{3-8}-cycloalkyl, NR^2, and CN; and

Z is selected from the group consisting of NR^1 and O;

or pharmaceutically acceptable salts and prodrugs.

2. The compound of claim 1, said compound selected from the group consisting of:



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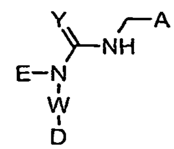


VII

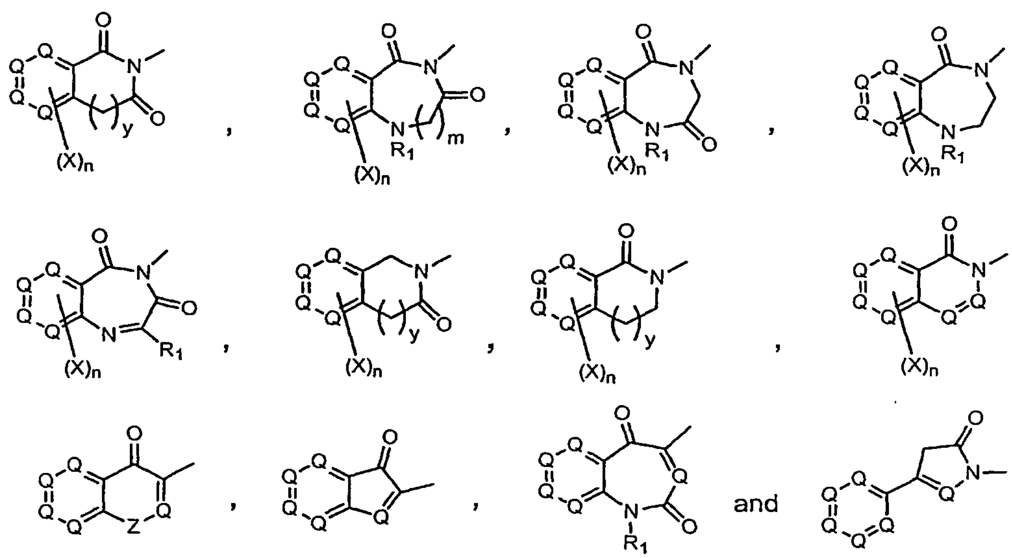
wherein:

A is selected from the group consisting of aryl, substituted aryl, heteroaryl, substituted heteroaryl, alkylaryl, and alkylheteroaryl;

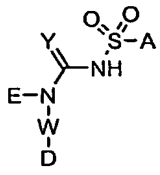
W is selected from the group consisting of aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

E is selected from the group consisting of H, $-C_1-C_8$ alkyl, polyhaloalkyl, $-C_{3-8}$-cycloalkyl, aryl, alkylaryl, substituted aryl, heteroaryl, and substituted heteroaryl;

D is selected from the group consisting of $-NR^1-(C{=}O)-R^2$, $-O-R^1$;



or alternatively, said compound is selected from the group consisting of:



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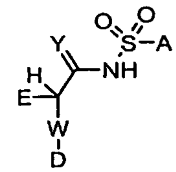

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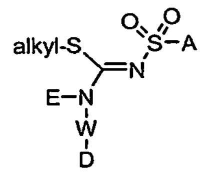

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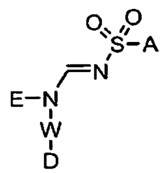

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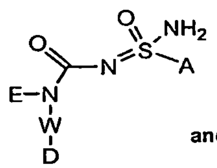
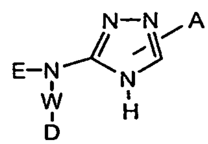


VI

and



VIII

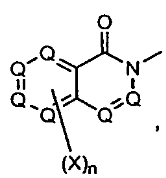
wherein:

A is selected from the group consisting of aryl, substituted aryl, heteroaryl, substituted heteroaryl, alkylaryl, and alkylheteroaryl;

W is selected from the group consisting of aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

E is selected from the group consisting of H, -C_1-C_8 alkyl, polyhaloalkyl, -$C_{3\text{-}8}$-cycloalkyl, aryl, alkylaryl, substituted aryl, heteroaryl, and substituted heteroaryl;

D is selected from the group consisting of -NR^1-(C=O)-R^2 , -O-R^1;



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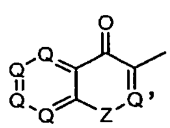

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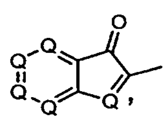

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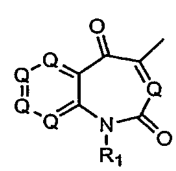

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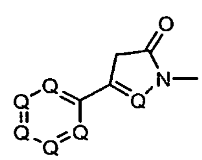


wherein, in either embodiment:

R^1 is independently selected from the group consisting of:

H, C_1-C_8 alkyl, polyhaloalkyl, -$C_{3\text{-}8}$-cycloalkyl, aryl, alkylaryl, substituted aryl, heteroaryl, substituted heteroaryl, -(C=O)-C_1-C_8 alkyl, -(C=O)-aryl, -(C=O)-substituted aryl, -(C=O)-heteroaryl and -(C=O)-substituted heteroaryl;

R^2 is independently selected from the group consisting of: aryl, substituted aryl, heteroaryl, and substituted heteroaryl, or

R^1 and R^2 can be direct linked or can be indirectly linked through a carbon chain that is from 1 to about 8 carbon atoms in length,

n is an integer from 0-4,

m is an integer from 0 or 1,

y is an integer from 0-4 and

Q is independently C or N, wherein when Q is a ring carbon atom, each ring carbon atom is independently substituted by X, wherein

X is in each case a member independently selected from the group consisting of: hydrogen, halogen, polyhaloalkyl, $-OR^3$, $-SR^3$, -CN, $-NO_2$, $-SO_2R^3$, $-C_{1-10}$-alkyl, $-C_{3-8}$-cycloalkyl, aryl, aryl-substituted by 1-4 R^3 groups, amino, amino-C_{1-8}-alkyl, C_{1-3}-acylamino, C_{1-3}-acylamino-C_{1-8}-alkyl, C_{1-6}-alkylamino, C_{1-6}-alkylamino C_{1-8} alkyl, C_{1-6} dialkylamino, C_{1-6} dialkylamino C_{1-8} alkyl, C_{1-6} alkoxy, C_{1-6} alkoxy-C_{1-6}-alkyl, carboxy-C_{1-6}-alkyl, C_{1-3}-alkoxycarbonyl, C_{1-3}-alkoxycarbonyl- C_{1-6}-alkyl, carboxy C_{1-6} alkyloxy, hydroxy, hydroxy C_{1-6} alkyl, and a 5 to 10 membered fused or non-fused aromatic or nonaromatic heterocyclic ring system, having 1 to 4 heteroatoms independently selected from N, O, and S, with the proviso that the carbon and nitrogen atoms, when present in the heterocyclic ring system, are unsubstituted, mono- or di- substituted independently with 0-2 R^4 groups,

wherein R^3 and R^4 are each independently selected from the group consisting of:
hydrogen, halogen, -CN, $-NO_2$, $-C_{1-10}$ alkyl, C_{3-8}-cycloalkyl, aryl, amino, amino-C_{1-8}-alkyl, C_{1-3}-acylamino, C_{1-3}-acylamino-C_{1-8}-alkyl, C_{1-6}-alkylamino, C_{1-6}-alkylamino C_{1-8} alkyl, C_{1-6} dialkylamino, C_{1-6} dialkylamino C_{1-8} alkyl, C_{1-6} alkoxy, C_{1-6} alkoxy-C_{1-6}-alkyl, carboxy-C_{1-6}-alkyl, C_{1-3}-alkoxycarbonyl, C_{1-3}-alkoxycarbonyl-C_{1-6}-alkyl, carboxy-C_{1-6}-alkyloxy, hydroxy, hydroxy-C_{1-6}-alkyl, -thio and thio-C_{1-6}-alkyl;

Y is selected from the group consisting of O, S, N-OR^5, and NR^5,

wherein R^5 is selected from the group consisting of :

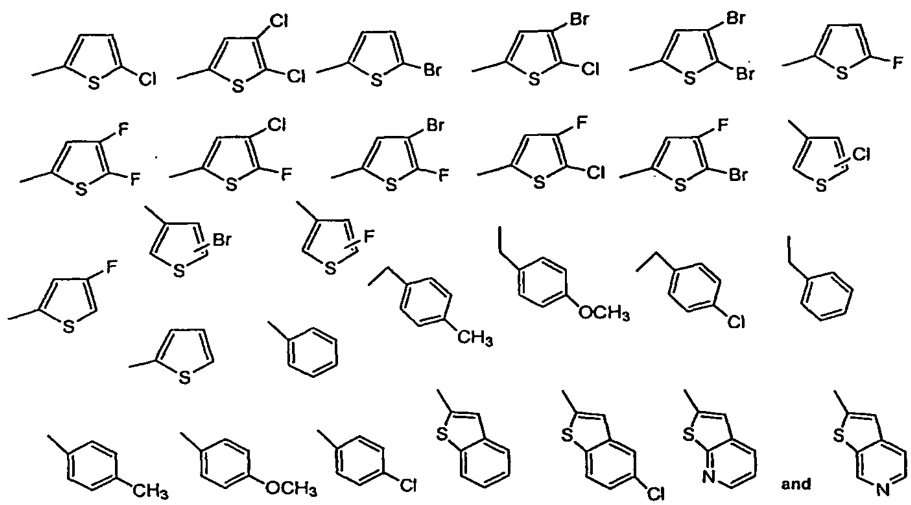
H, C $_{1-10}$ alkyl, C $_{3-8}$-cycloalkyl, NR^2, and CN; and

Z is selected from the group consisting of NR^1 and O;

or pharmaceutically acceptable salts and prodrugs.

3. The compound of claim 1, wherein:

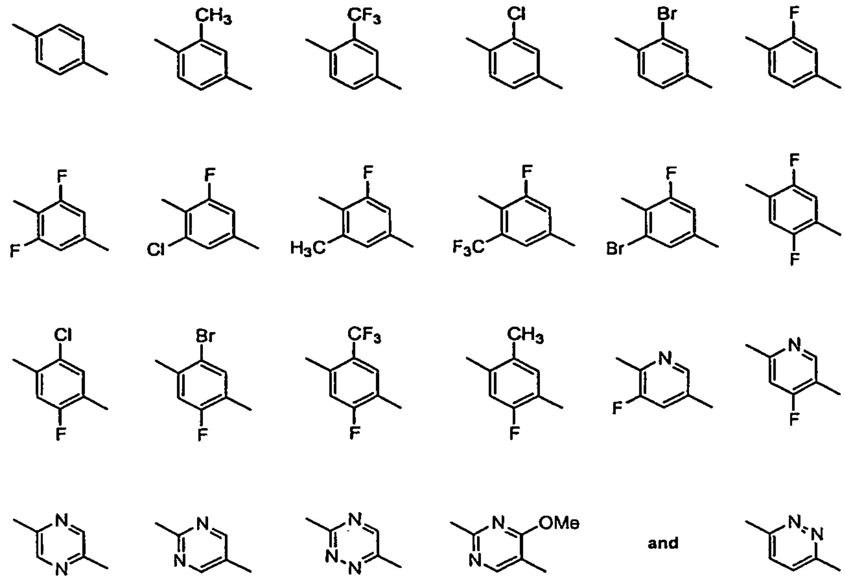
A is selected from the group consisting of:



Y is selected from the group consisting of O, S, N-OR^5 and NR^5.

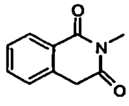
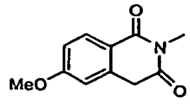
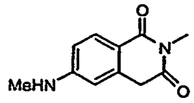
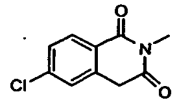
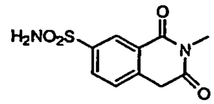
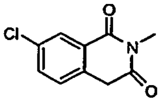
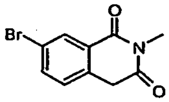
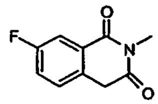
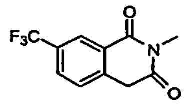
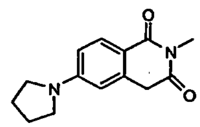
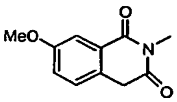
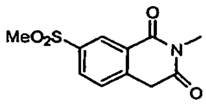
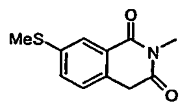
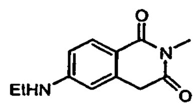
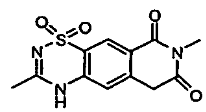
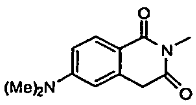
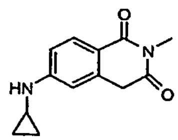
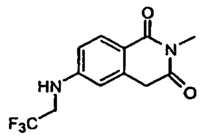
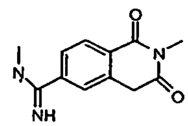
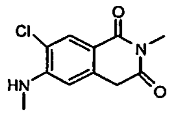
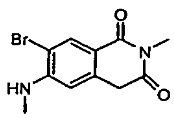
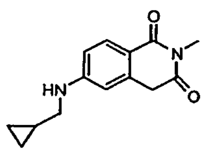
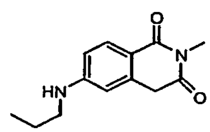
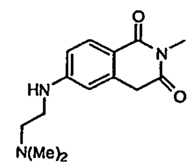
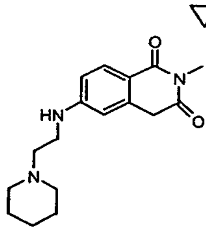
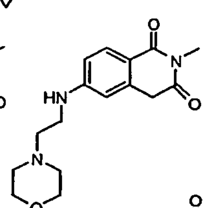
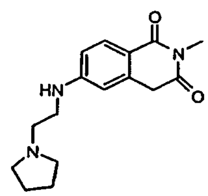
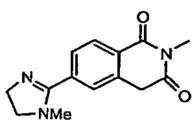
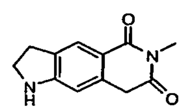
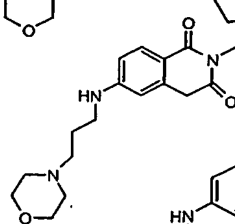
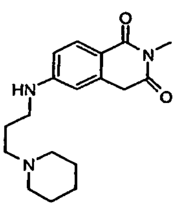
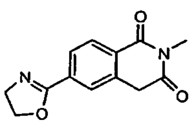
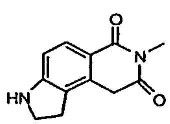
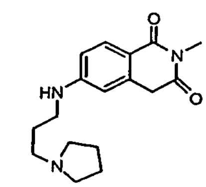
E is selected from the group consisting of H, or C$_{1-8}$ alkyl.

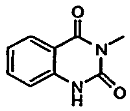
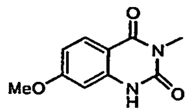
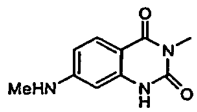
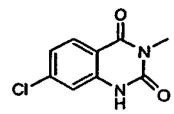
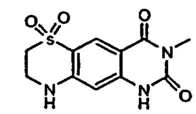
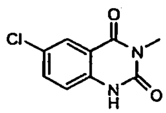
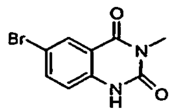
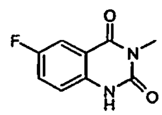
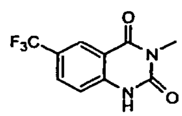
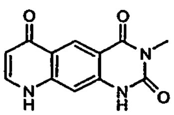
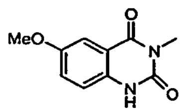
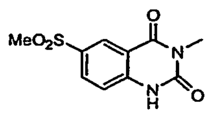
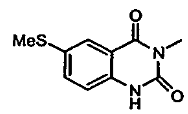
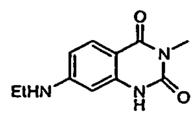
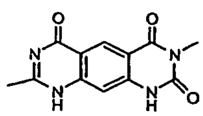
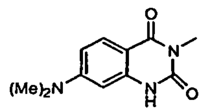
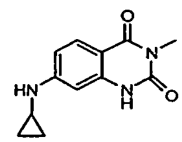
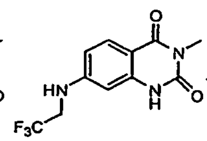
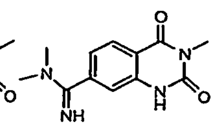
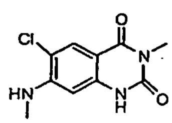
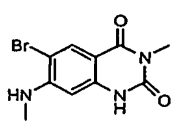
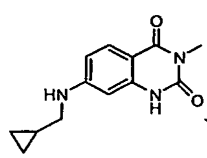
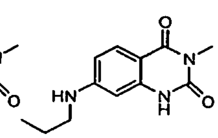
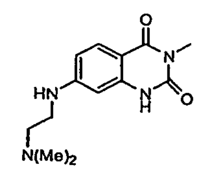
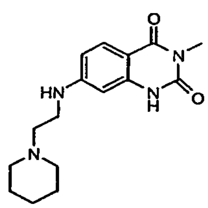
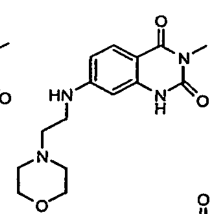
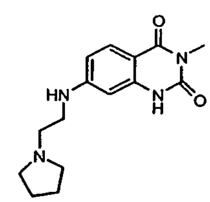
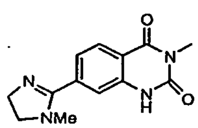
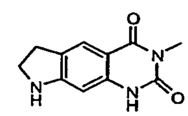
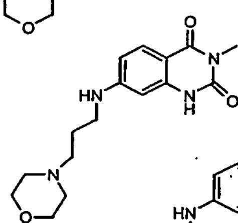
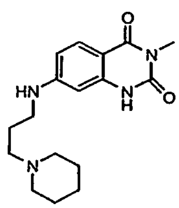
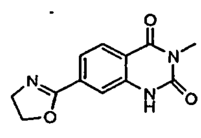
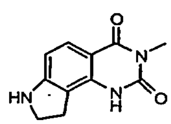
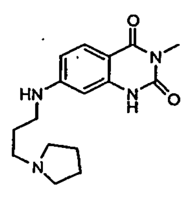
W is selected from the group consisting of:

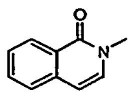
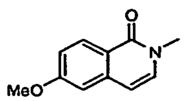
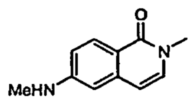
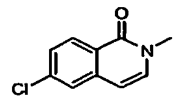


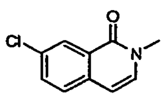
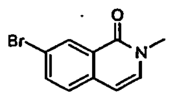
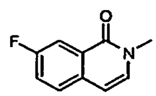
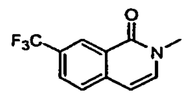
4. The compound of claim 1, wherein:

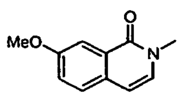
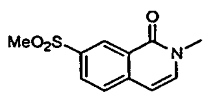
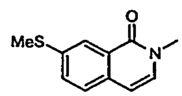
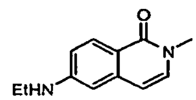
D is selected from the group consisting of:

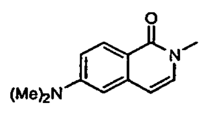
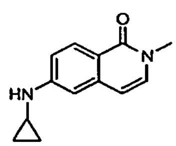
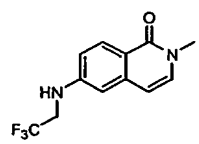
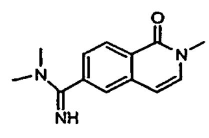



































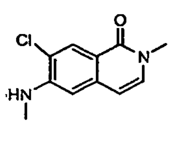
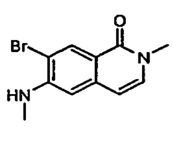
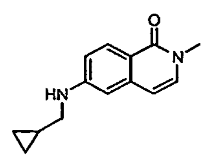
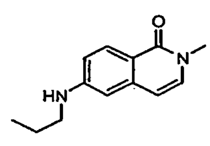



































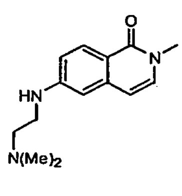
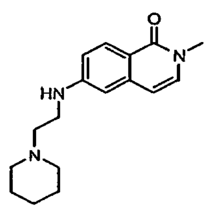
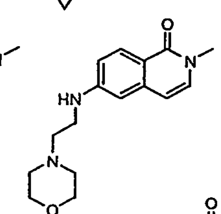
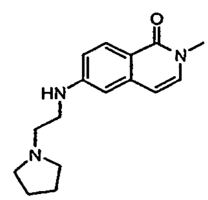
   

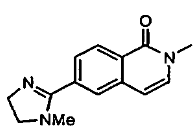
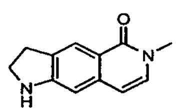
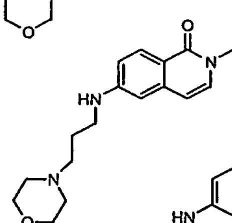
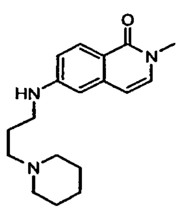
   

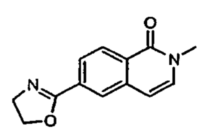
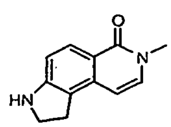
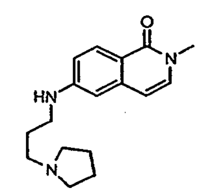
   

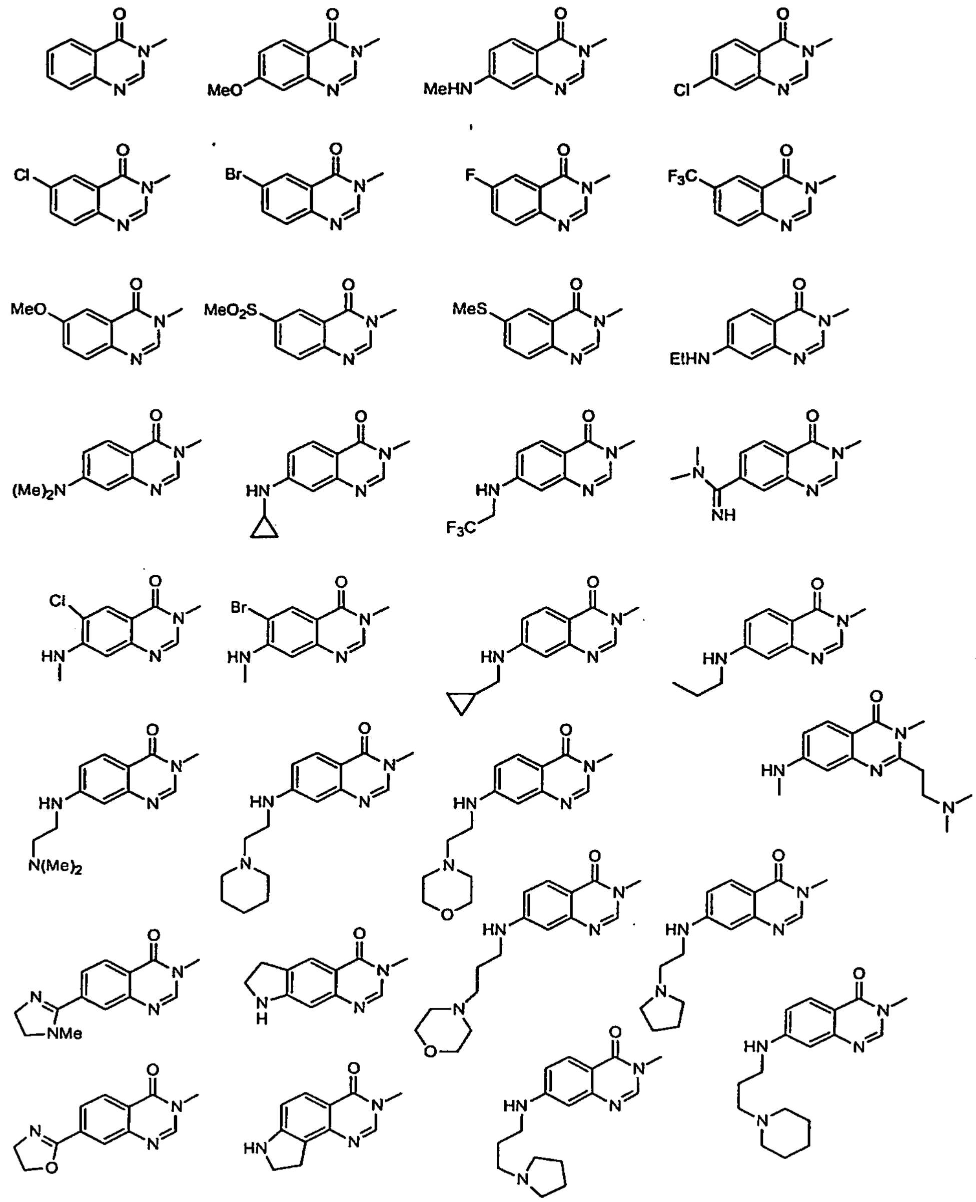
   

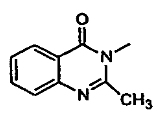
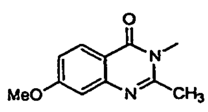
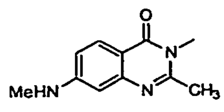
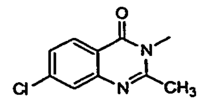
   

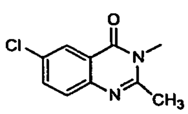
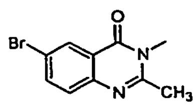
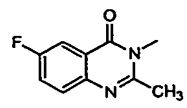
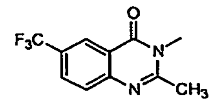
   

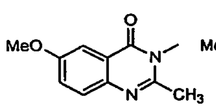
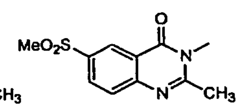
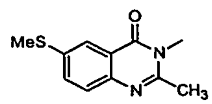
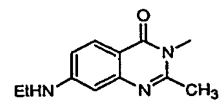
   

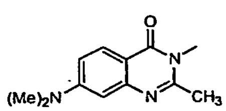
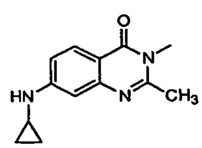
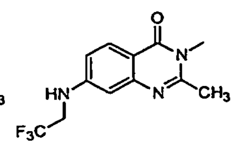
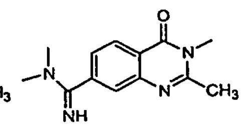
  

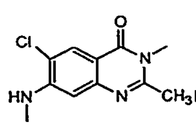
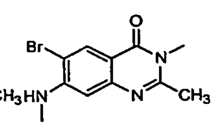
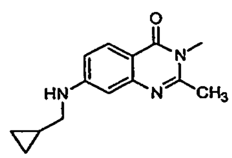
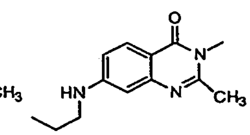


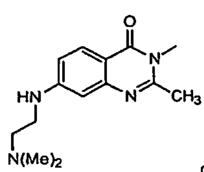
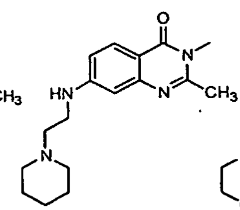
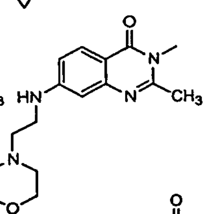
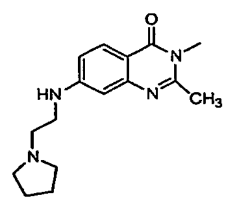
   

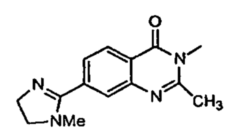
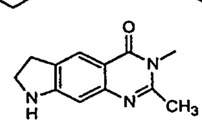
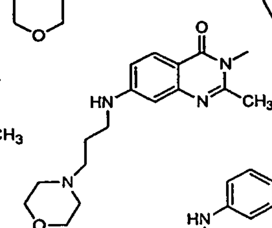
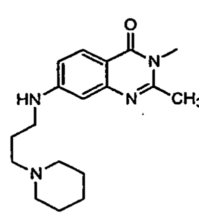
   

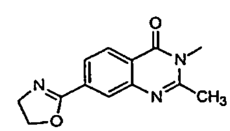
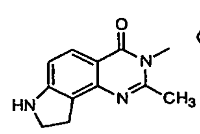
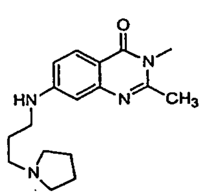
   

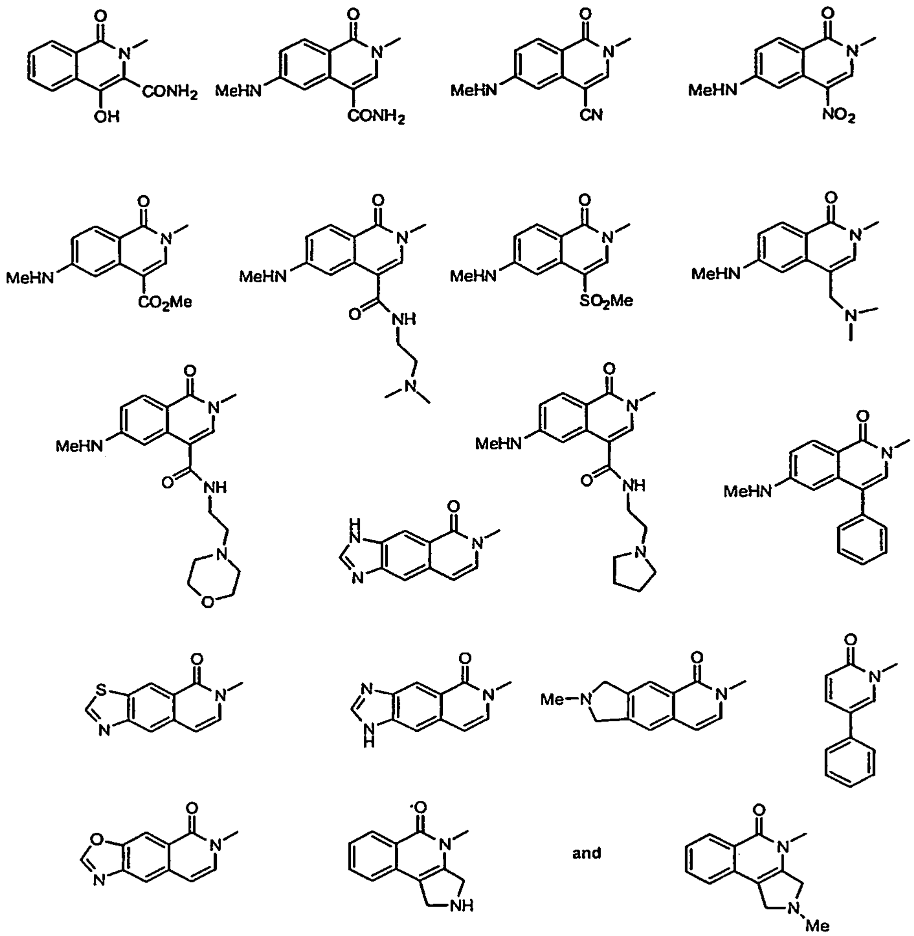
   

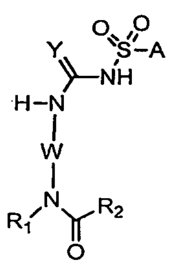
   

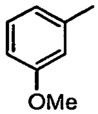
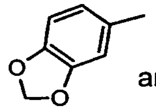
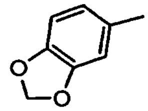


5. The compound of claim 1, having the following formula:

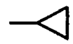


wherein:

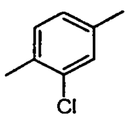
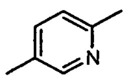
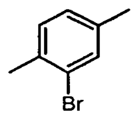
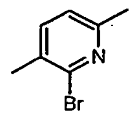
R_2 is selected from the group consisting of:

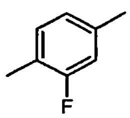
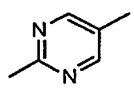
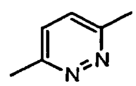
, ,  and ,

R_1 is selected from the group consisting of:

H, Me and ,

W is selected from the group consisting of:

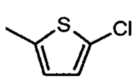
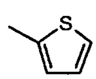
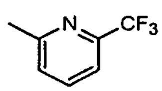
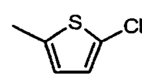
, , , ,

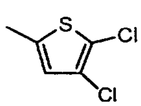
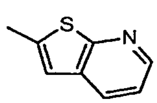
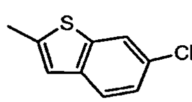
,  and 

Y is selected from the group consisting of:

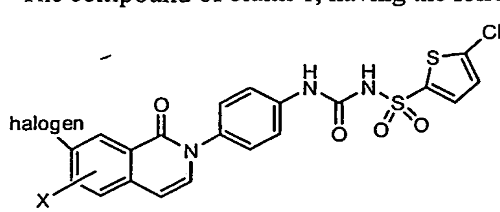
O, S, N-C≡N, NH and N-OH, and

A is selected from the group consisting of:

, , , ,

,  and .

6. The compound of claim 1, having the following formula:

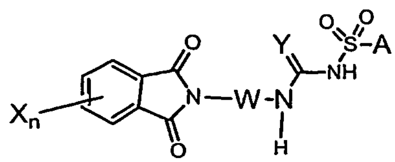


wherein:

halogen is selected from the group consisting of: Br, F, Cl, and I; and

X is selected from the group consisting of C_{1-8} alkyl, and –NH-alkyl.

7. The compound of claim 1, having the following formula,



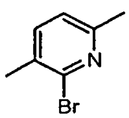
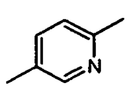
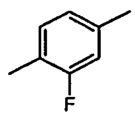
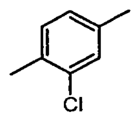
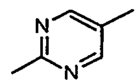
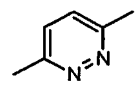
wherein:

n is an integer from 0-4;

X is selected from the group consisting of:

3-Br, 3-Cl, 4-OMe, H, 3-SO_2Me, 3-N(Me)$_2$ and 3,4,-dimethyl;

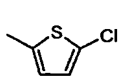
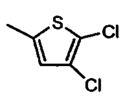
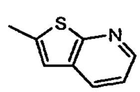
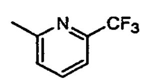
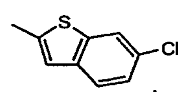
W is selected from the group consisting of:

 ,  ,  ,  ,  and 

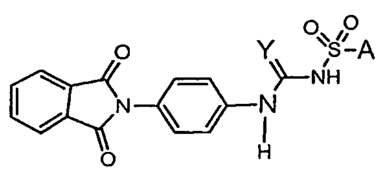
Y is selected from the group consisting of:

O , N-C≡N , NH and N/OH

A is selected from the group consisting of:

 ,  ,  ,  , and  .

8. The compound of claim 1, having the following formula:

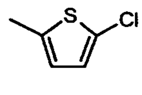
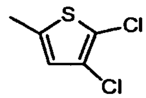
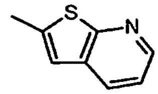


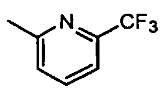
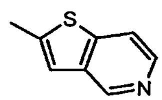
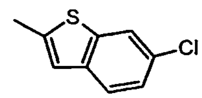
wherein:

Y is selected from the group consisting of:

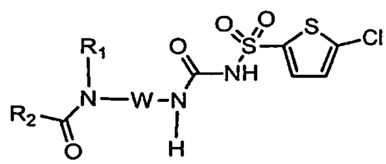
O , N-C≡N , NH and N/OH

A is selected from the group consisting of:

 ,  ,  ,

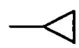
 ,  and 

9. The compound of claim 1, having the following formula:

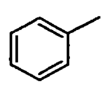
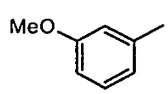
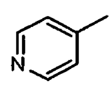
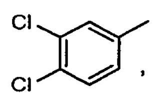
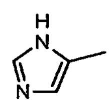
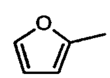


wherein

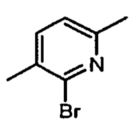
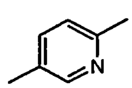
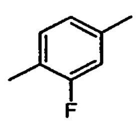
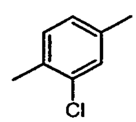
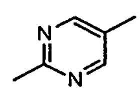
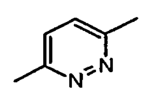
R_1 is selected from the group consisting of:

H , Me and 

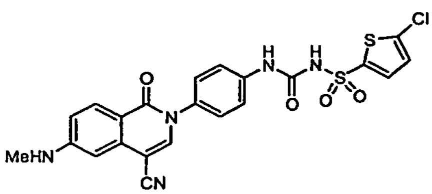
R_2 is selected from the group consisting of:

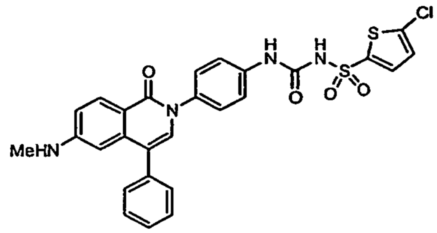
 ,  ,  ,  ,  and 

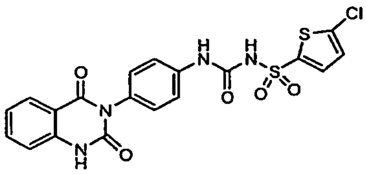
W is selected from the group consisting of:

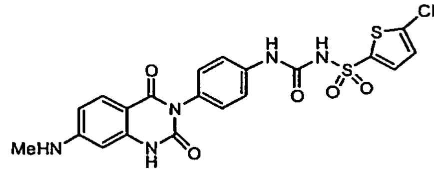
 ,  ,  ,  ,  and 

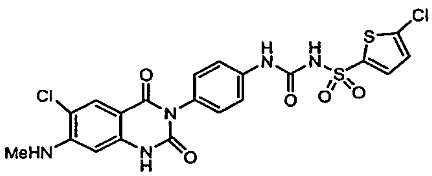
10. The compound of claim 1, selected from the group consisting of:

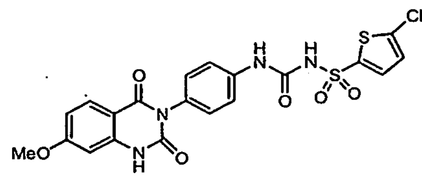


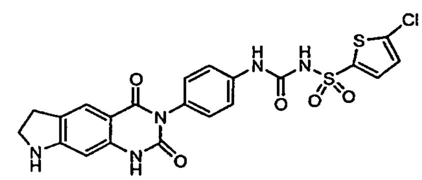


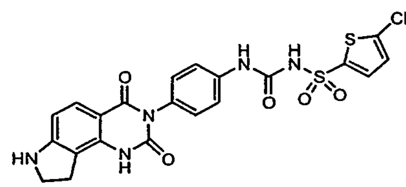


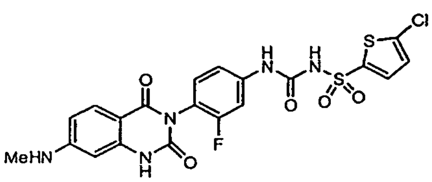


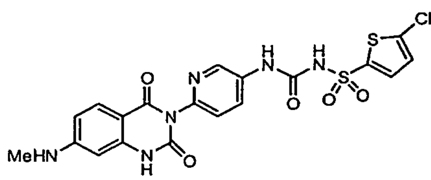


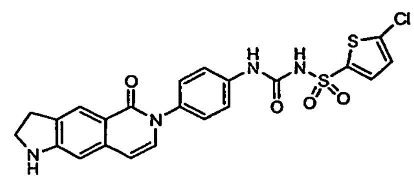


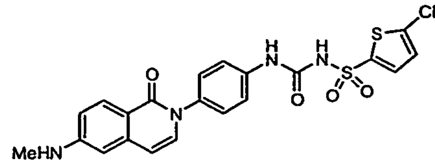


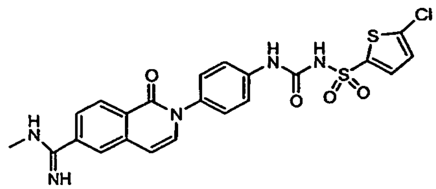


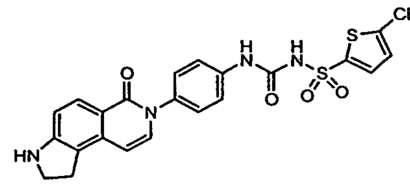


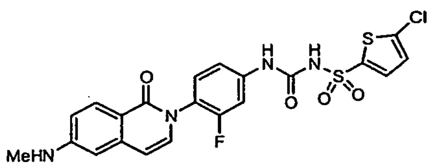


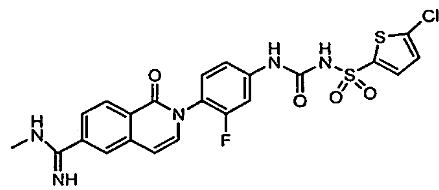


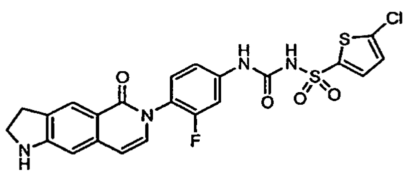


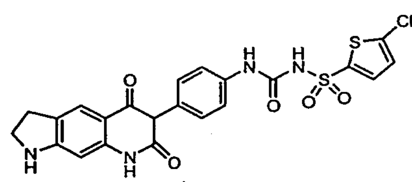


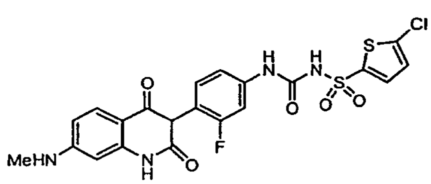


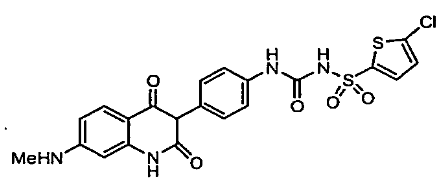












11. The pharmaceutical composition for preventing or treating thrombosis in a mammal comprising a therapeutically effective amount of a compound according to claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

12. The pharmaceutical composition of claim 11, wherein said therapeutically effective amount is an amount effective to inhibit platelet aggregation in the mammal.

13. A pharmaceutical composition of claim 12, wherein said platelet aggregation is platelet ADP-dependent aggregation.

14. The pharmaceutical composition of claim 13, wherein said mammal is a human.

15. The pharmaceutical composition of claim 11, wherein said compound is an effective inhibitor of [^{3}H]2-MeS-ADP binding to platelet ADP receptors.

16. The pharmaceutical composition for preventing or treating thrombosis in a mammal comprising a therapeutically effective amount of a compound according to claim 8, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

17. The pharmaceutical composition of claim 16, wherein said therapeutically effective amount is an amount effective to inhibit platelet aggregation in the mammal.

18. The pharmaceutical composition of claim 17, wherein said platelet aggregation is platelet ADP-dependent aggregation.

19. The pharmaceutical composition of claim 18, wherein said mammal is a human.

20. The pharmaceutical composition of claim 16, wherein said compound is an effective inhibitor of [^{3}H]2-MeS-ADP binding to platelet ADP receptors.

21. The method for preventing or treating thrombosis in a mammal comprising the step of administering to a mammal a therapeutically effective amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof.

22. The method of claim 21, wherein said mammal is a human.

23. The method of claim 21, wherein said mammal is prone to or suffers from a cardiovascular disease.

24. The method of claim 21, wherein said cardiovascular disease is at least one selected from the group consisting of acute myocardial infarction, unstable

angina, chronic stable angina, transient ischemic attacks, strokes, peripheral vascular disease, preeclampsia/eclampsia, deep venous thrombosis, embolism, disseminated intravascular coagulation and thrombotic cytopenic purpura, thrombotic and restenotic complications following invasive procedures resulting from angioplasty, carotid endarterectomy, post CABG (coronary artery bypass graft) surgery, vascular graft surgery, stent placements and insertion of endovascular devices and prostheses.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/23909

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D521/00 C07D409/12 C07D209/48 A61K31/4035 A61P7/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, EPO-Internal, WPI Data, BEILSTEIN Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 01 57037 A (COR THERAPEUTICS INC) 9 August 2001 (2001-08-09) page 1, line 3 - line 10; claim 1 ---	1-24
X	WO 99 36425 A (COR THERAPEUTICS INC) 22 July 1999 (1999-07-22) cited in the application page 1, line 1 - line 7; claim 1 ---	1-24
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 October 2002	18/10/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Seelmann, I

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; PLOTNIKOVA, M. T. ET AL: "Arenesulfonamides. LXXX. Aroylarenesulfonamides" retrieved from STN Database accession no. 82:139564 XP002215531 abstract & VOPR. KHIM. KHIM. TEKHNOL. (1974), 33, 20-5 ,	1

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

The present claims relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds of formula I, II, IV, VI and VII, with D = 1,3-dioxobenzo'c!azolidin, 2,4-dioxo-1,3-dihydroquinazolin, benzamide, 1-oxo-2-hydroisoquinolin and 4-oxo-3-hydroquinazolin (according to the examples as given on pages 158-222).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

I..._...ational application No.
PCT/US 02/23909

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

Inte   nal Application No
PCT/US 02/23909

Patent document cited in search report		Publication date	Patent family member(s)			Publication date
WO 0157037	A	09-08-2001	AU	3664401	A	14-08-2001
			WO	0157037	A1	09-08-2001
			US	2002025961	A1	28-02-2002
			US	2002077486	A1	20-06-2002
WO 9936425	A	22-07-1999	AU	2219599	A	02-08-1999
			CA	2318199	A1	22-07-1999
			EP	1047699	A1	02-11-2000
			JP	2002509152	T	26-03-2002
			WO	9936425	A1	22-07-1999